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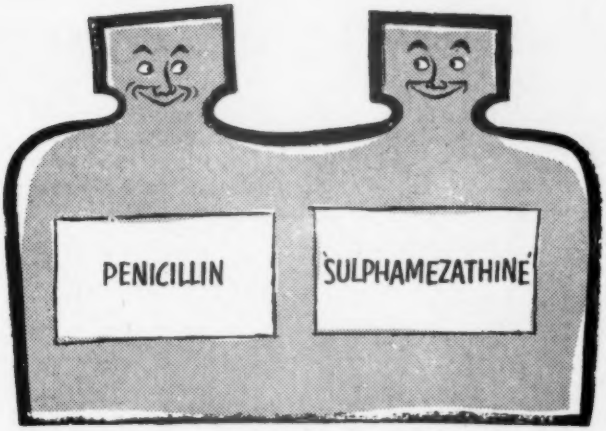

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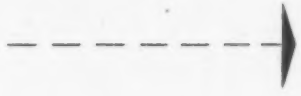

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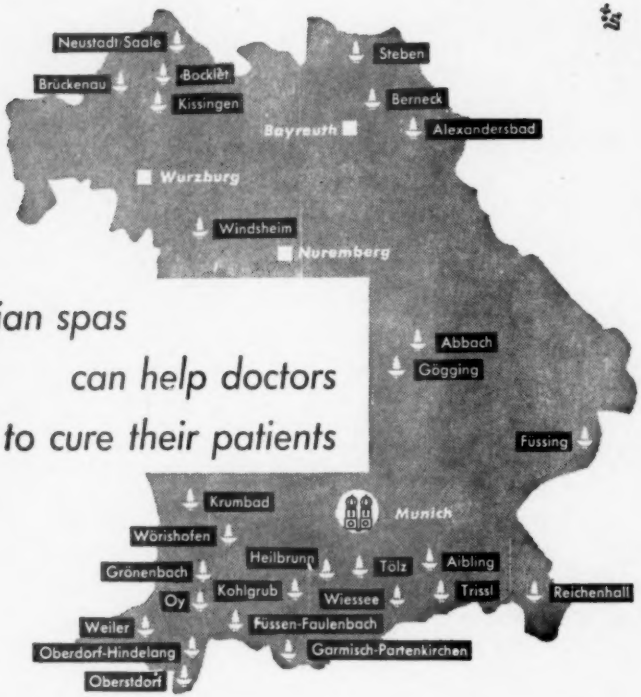

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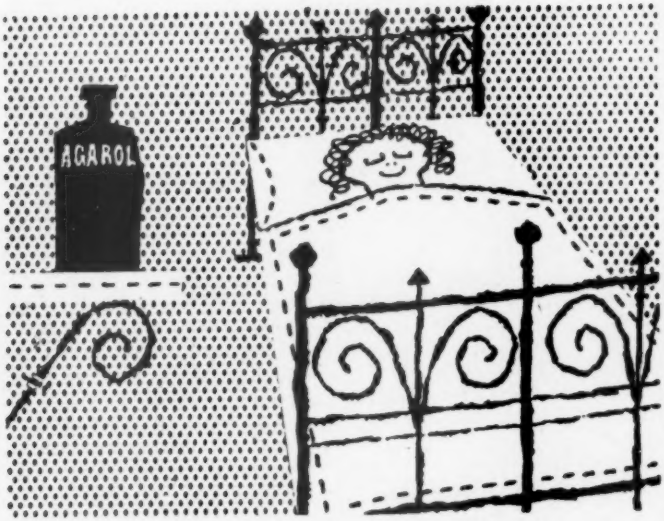

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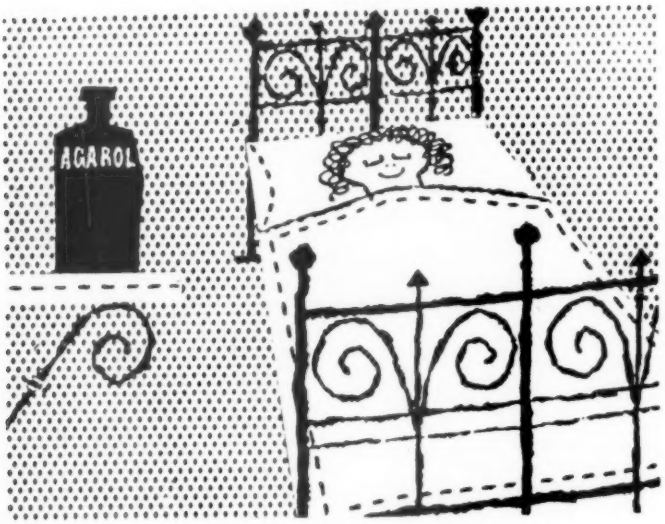

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The Control of Gastric Acidity. *Brit. Med. J.* 26th July, 1952, **2**: 180-182. Medical Treatment of Peptic Ulcer. *Med. Press* 27th February, 1952, **227**: 195-199. Notes on Remedial Agents. *Med. Rev.* September, 1952, **46**: 162. Discussion on Peptic Ulceration. *Proc. Roy. Soc. Med.* May 1953, **46**: 354. The Effect on Gastric Acidity of "Nulacin" tablets. *Med. J. Aust.* 28th November, 1953, **2**: 823-824. Control of Gastric Acidity by a New Way of Antacid Administration. *J. Lab. Clin. Med.* 1953, **42**: 955. Further Studies on the Reduction of Gastric Acidity. *Brit. Med. J.* 23rd January, 1954, **1**: 183-184. Clinical Investigation into the Action of Antacids. *The Practitioner* July, 1954, **173**: 46. Management of Peptic Ulceration in General Practice. *Med. World* December, 1954, **81**: 591-601. Ambulatory continuous Drip Method in the Treatment of Peptic Ulcer. *Amer. J. Dig. Dis.* March, 1955, **22**: 67-71. Notes on Remedial Agents. *Med. Rev.* October, 1955, **49**: 142. Antacids in Peptic Ulcer. *The Practitioner*, January, 1956, **176**: 103.

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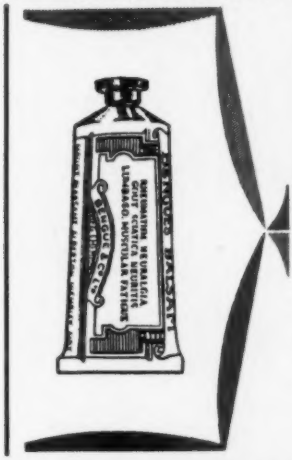

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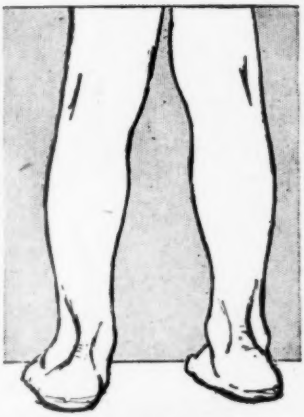

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a positive advance in theophylline therapy

- A pure chemical compound — theophylline ethanoate of piperazine
- Soluble — Stable — Neutral
- Seven times less toxic than theophylline itself
- Freely tolerated orally for long-term therapy without nausea, vomiting or gastric disturbance
- Intramuscular injections of Etophylate are painless

Etophylate is indicated for the treatment of cardiac, respiratory and renal conditions

ETOPHYLATE

Clinical reports and samples gladly sent on request

Presentation: Tablets, 250 mg., in bottles of 25, 100 and 500.
Suppositories, 500 mg., in boxes of 12 and 144.
Ampoules, 500 mg. in 5 cc., in boxes of 6 and 50.

Etophylate is also available with phenobarbitone and papaverin

RONA LABORATORIES

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PRELUDIN makes the task of the practitioner both simple and safe when dealing with cases of obesity.
PRELUDIN is an appetite controlling agent which rapidly breaks the habit of overeating and enables the patient to adhere to a recommended diet without effort. Because it does not affect the heart or the blood pressure it is particularly suitable in cases of cardiovascular disorders or hypertension.
PRELUDIN is supplied in 25 mg. tablets, in tubes of 20 or bottles of 250.

PRELUDIN* The appetite controlling agent that does not affect the heart

Brand of 2-phenyl-3-methyl-tetrahydro-1, 4-oxazine-hydrochloride

Manufactured and distributed in England by Pfizer Ltd., Folkestone, Kent, for
C. H. Boehringer Sohn, Ingelheim am Rhein
Registered proprietors of the Trade Mark *Regd. Trade Mark

Deltalgycortril*

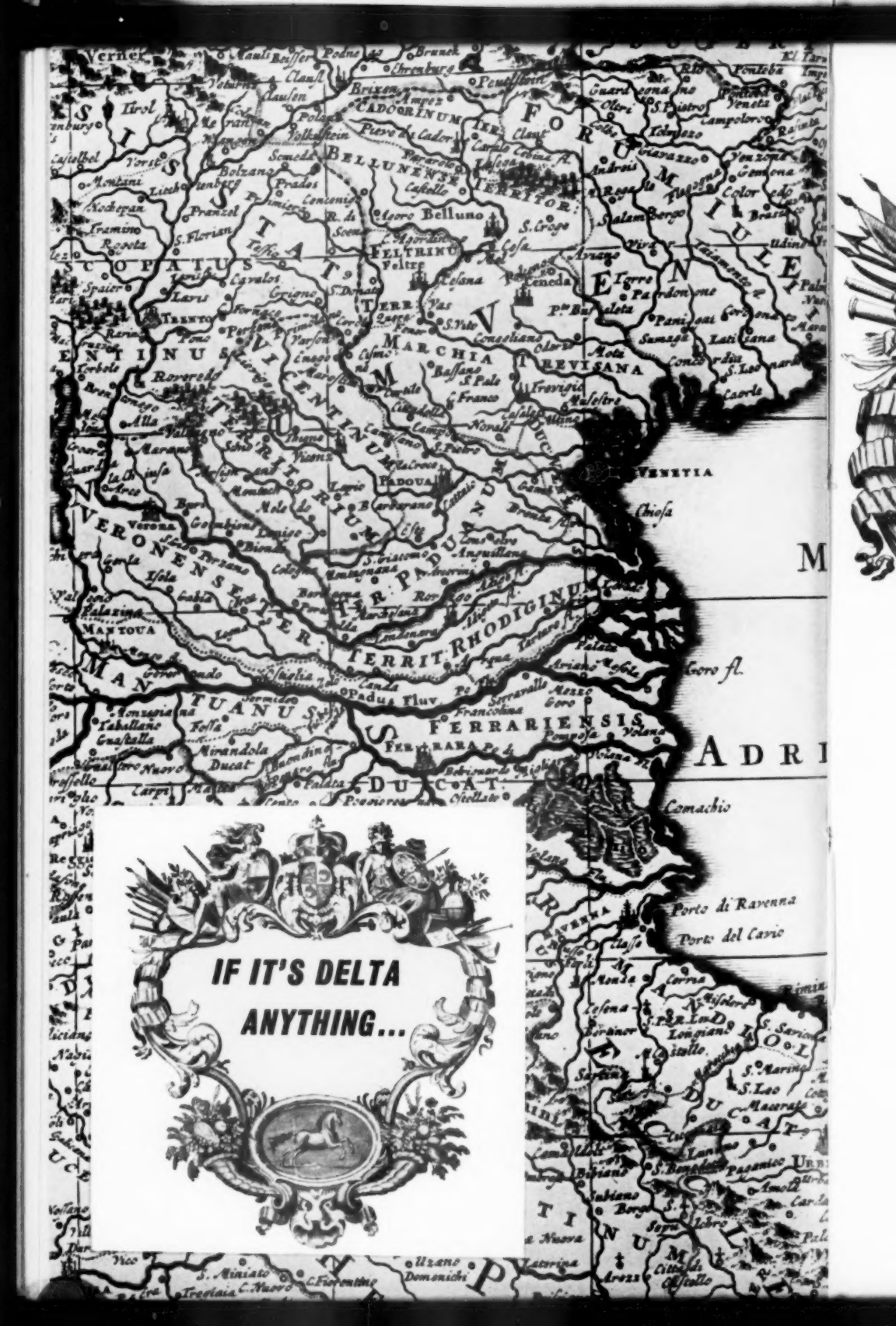
AN IMPROVED ANTI-RHEUMATIC AGENT

Deltalgycortril combines the anti-inflammatory and anti-rheumatic action of Deltacortril*, the newest corticosteroid, with the established analgesic effect of acetylsalicylic acid. It has been said that "With such a combination the palliative management of the rheumatic diseases may be undertaken in many cases without encountering the side effects and undesirable reactions seen in high dose salicylate or adrenal steroid therapy when used alone."[1]

[1] *Ohio State Med. J.*, (1956), **52**, 722.

Deltalgycortril tablets, each of which contains 0.5 mg of Deltacortril and 5 grains of acetylsalicylic acid, are available in bottles of 100.

Pfizer PFIZER LTD · FOLKESTONE · KENT *Trade Marks of Chas. Pfizer & Co., Inc.


IF IT'S DELTA
ANYTHING...

IT'S

Deltacortril*

BRAND OF PREDNISOLONE

Pfizer PFIZER LTD · FOLKESTONE · KENT

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DELTACORTRIL is a new synthetic steroid for superior systemic anti-rheumatic, anti-allergic and anti-phlogistic therapy

DELTACORTRIL is 3 to 5 times more potent than hydrocortisone or cortisone and is more effective than prednisone

DELTACORTRIL achieves maximal response at fractional dosage

DELTACORTRIL offers superior therapy in asthma and dermatitis and is markedly effective where other corticosteroids have failed

DELTACORTRIL brings rapid and prolonged relief of arthritic symptoms

DELTACORTRIL therapy is marked by virtual absence of sodium or water retention and consequently causes no weight gain, oedema or hypertension

DELTACORTRIL does not cause excessive potassium loss

DELTACORTRIL 1 mg. tablets are supplied in bottles of 100 and 5 mg. scored tablets in bottles of 10, 20, 100, 500 and 1,000.

Pfizer, the world's largest producer of antibiotics, announce the introduction of Sigmamycin. This is a 2 : 1 combination of tetracycline and the newly-discovered medium-spectrum antibiotic oleandomycin. It has been clearly shown, both *in vitro* and *in vivo*, that this combination demonstrates synergism.

Sigmamycin capsules contain 167 mg. tetracycline and 83 mg. oleandomycin. Available in bottles of 16 and 100.

depth in the broad spectrum

Pfizer *World's largest producer of antibiotics.*

PFIZER LTD · FOLKESTONE · KENT

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relieving the agony of spasm

BUSCOPAN is a selective spasmolytic agent which affects specifically the hollow organs of the abdomen and the genito-urinary tract. BUSCOPAN relieves spasm, smoothly and quickly without producing unpleasant side effects. Many painful conditions, such as gastric and duodenal ulcer, spastic dysmenorrhœa and renal or biliary colic will respond readily to its action. Its administration often enables accurate differentiation to be made between spasmodic and organic obstruction.

INGELHEIM

BUSCOPAN*

HYOSCINE-N-BUTYLBROMIDE

Manufactured and distributed in England by Pfizer Ltd., Folkestone, Kent, for

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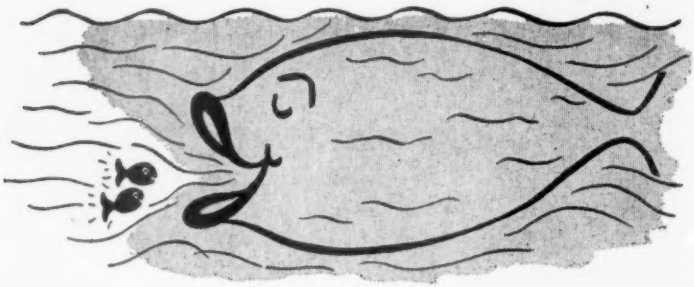
Registered proprietors of the Trade Mark

**Registered Trade Mark*

The original easy-to-take, two-in-one tablet

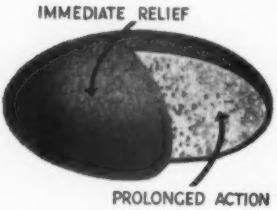


for the prompt and prolonged relief of ASTHMA

ISO-BRONCHISAN was first produced in 1953 and offers a fresh approach to the problem of effective asthma control. The tablets, which are pleasant to take, have a coating containing easily dissolved Isopropyl-Nor-Adrenaline, a most potent bronchodilator, which, when absorbed by the sublingual route, produces the prompt relief of bronchospasm. The rest of the tablet, when swallowed, releases Ephedrine and Theophylline in balanced proportions and these, slowly absorbed along the alimentary tract, ensure long sustained antispasmodic action on the bronchial smooth muscle.

ISO-BRONCHISAN

Prescribable on Form E.C. 10.



SILTEN

Each tablet contains Isopropyl-Nor-Adrenaline (Isoprenaline) sulphate gr. ¼; Ephedrine hydrochlor. gr. 2/5; Theophylline gr. 2. In tubes of 20 tablets and bottles of 100 tablets. *Tablets containing smaller quantities of the effective ingredients are now available for use in Paediatrics.*

Samples and literature available on request:

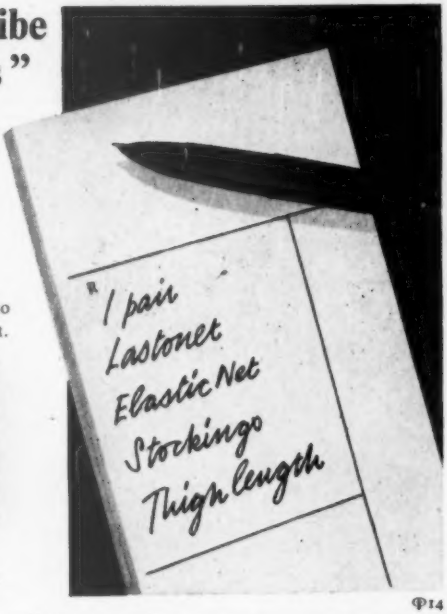
SILTEN LIMITED · SILTEN HOUSE · HATFIELD · HERTS · ENGLAND

"I'm going to prescribe Lastonet stockings"

And this is how to do it. The words "ELASTIC NET STOCKINGS" *must* be written on the E.C.10 to obtain Lastonet stockings for supply under the Ministry of Health scheme. The quantity required and whether thigh or knee length should also be included. The correct wording is important to secure Lastonet stockings which are made only to *individual* measure and so ensure a perfect fit.

IN **NYLON** OR COTTON

LASTONET PRODUCTS LTD., CARN BREA, REDRUTH, CORNWALL



Φ14

Ancestral habits...

When the Mediaeval King put aside his arms and stood alone, coldly footing it in chilly castle chamber, why the frowning concern with hair? Was it the scalp worry of all ages? Dandruff?

Sebaceous glands being the secretory things they are, there was then no royal remedy for the regal irritation. But today the old and familiar trouble has been mastered by SEBODERM, the Cetrimide Shampoo specifically for Dandruff.

Seboderm contains 15.6% of Cetrimide B.P., the quaternary ammonium prescribed as most effective against dandruff. Normally a single weekly treatment is sufficient to establish complete control.

Seboderm also contains 15.6% Cetyl Alcohol B.P. and 1% Lanolin, and as a finely emulsified, creamy shampoo it leaves the scalp free from irritation and the hair soft, silky and clean

Seboderm masters Dandruff

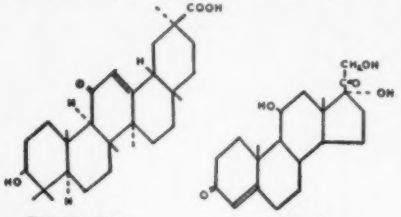
Professional sample will be gladly sent on request

PRIORY LABORATORIES LIMITED
WEST DRAYTON MIDDLESEX

A new anti-inflammatory and anti-pruritic agent

BIOSONE G.A.

BIOSONE G.A. PREPARATIONS contain the active isomers of Glycyrrhetinic Acid which, when applied to the skin, has an action resembling that of HYDROCORTISONE (B.M.J., Dec. 1955, p. 1501, LANCET, July 1956, p. 145).



Glycyrrhetic Acid
Glycyrrhetinic Acid

Hydrocortisone

Available as:—

BIOSONE G.A. Ointment "GREASY"

BIOSONE G.A. Ointment "NON-GREASY"

BIOSONE G.A. Ointment with NEOMYCIN

BIOSONE G.A. OPHTHALMIC Ointment and with NEOMYCIN

BIOSONE G.A. Compound SUPPOSITORIES

BIOSONE G.A. SNUFF

BIOSONE G.A. is INEXPENSIVE by comparison with Hydrocortisone and no systemic or local reactions have been reported.

BIOSONE G.A.

The FIRST CHOICE in the treatment of inflammatory conditions

FREELY PRESCRIBABLE ON E.C.10

Samples and literature available on request.

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For 40 years

"EUPINAL"

has been used successfully in the treatment of ASTHMA and CHRONIC BRONCHITIS and may be prescribed on N.H.S. Form E.C. 10

"Eupinal" contains Iodine and Caffeine combined in a most elegant and effective form.

In chronic Bronchitis "Eupinal" softens the tough accumulated mucus in the bronchial tubes and allows it to be more readily expectorated. In Asthma it possesses a more markedly soothing effect, lessening the frequency of attacks and reducing their severity and duration, and relieving breathlessness.

"Eupinal" contains no poison and is safe in use.

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THE SAFEST AND BEST PREPARATION OF OPIUM

Nepenthe contains all the constituents of opium and has been prescribed for over 100 years. It has been found by generations of Practitioners to be the best preparation of Opium as it does not cause the unpleasant after-effects usually attributed to opiates. It can be given over a considerable period and the effect remains invariably constant.

Packed in 2-oz., 4-oz., 8-oz. and 16-oz. bottles and for injection in ½-oz. rubber-capped bottles, sterile, ready for use.

NEPENTHE

Regd.

FERRIS & CO LTD

BRISTOL

Tel: 21381 Grams: Ferris, Bristol

Canned strained foods set a mother's mind at rest

As you know, some mothers are worried when you advise early mixed feeding for baby. With so many other things to do, the difficulty of obtaining and preparing a variety of fresh foods seems almost insuperable. But Heinz Strained Foods solve the mother's problem and make it easy for her to follow your advice.

Furthermore, Heinz Strained Foods are better for baby than many home-prepared foods. Heinz get their vegetables and fruits straight from farms. And the special Heinz cooking and straining equipment preserves the maximum goodness.

So with 19 really nourishing varieties to choose from, it's easy for mother to give her baby the varied diet you recommend.

For a FREE booklet giving the nutrient values of all 19 varieties of Heinz Strained Foods, please write to Dept. 7R, H. J. Heinz Company Ltd., London N.W.10.

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SOUPS · MEAT BROTHS · VEGETABLES · SWEETS · CEREAL

SEA-PEARLS

the new small fish-oil capsules

Children especially will find SEA-PEARLS easier to swallow because they are so small. The capsules are seamless and ensure the fish-oil content is kept in good condition over a long period. Only finest blended fish liver oils are used—to provide a well balanced vitamin content in a remarkably small capsule. Supply is in tins of 100 which release one capsule at a time. Price 5/- per 100.

EACH CAPSULE PROVIDES 4,500 I. UNITS VITAMIN A AND 450 I. UNITS VITAMIN D

Manufactured by A/S APOTHEKERNES LABORATORIUM, SKÖYEN PR. OSLO, NORWAY.

Sole Distributors for Great Britain:
MAYBORN PRODUCTS LTD.,
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The Ambulatory Treatment of Ulceration of the leg

The plaster used in the manufacture of "Lestreflex" is innocuous to newly formed tissue cells and leucocytes and the bandage is unsurpassed in the ambulatory treatment of ulceration of the leg. It provides a means of alleviating pain and promoting rapid healing. This bandage is often successful where allergy to other bandages has arisen.
"Lestreflex" is also available with strip ventilation, assuring aeration to the wound.

LESTREFLEX
ELASTIC DIACHYLON BANDAGE
AVAILABLE ON E.C.10

Write for booklet describing ambulatory treatment of ulceration of the leg.

DALMAS
WATERPROOF FIRST AID DRESSINGS

The Dalmas Doctor's Cabinet contains 180 waterproof dressings in eight sizes and shapes plus a one-yard spool of Dalmas Strapping.
Full details and samples available on request.

DALMAS
DALMAS LIMITED, LEICESTER & LONDON. Est. 1823
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The "Cestra" Mask
FOR SURGEONS AND NURSES

Bacteriologically tested and specially designed for the prevention of droplet infection

After many bacteriological experiments this mask was designed to arrest all droplets from the mouth and nose, and so to prevent contamination during operation. The "Cestra" Mask consists of four layers of fine dental gauze. It fastens securely under the chin, has an air gap at the sides, is comfortable to wear for long periods and may be easily sterilised.

Obtainable from Chemists and Medical Stores
MADE BY ROBINSON & SONS LTD.
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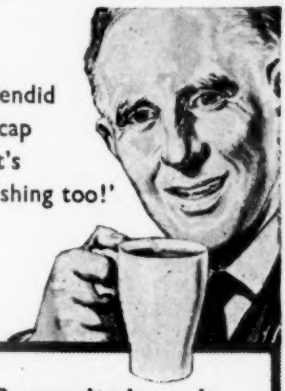
Manufacturers of all kinds of Surgical Dressings

'A splendid nightcap and it's nourishing too!'



Bourn-vita is made from malt, milk, sugar, cocoa and eggs

sleep sweeter
BOURN-VITA
made by CADBURYS

B12

with

INTRINSIC FACTOR

for oral administration

BIOPAR FORTE is the outcome of years of ARMOUR RESEARCH to combine Vitamin B12 with a much more potent intrinsic factor than hitherto, and to provide an effective oral therapy to replace injected B12 for Pernicious Anaemia.

CLINICALLY EFFECTIVE in: Pernicious Anaemia and other macrocytic anaemias; Sprue; Growth Retardation; Anorexia; Polyneuritis; Diabetic and Alcoholic Neuritis; Osteoarthritis and Osteoporosis; Trigeminal Neuralgia; Migraine; Herpes Zoster.

Each Biopar Forte Tablet contains 35 mg. Intrinsic Factor and 15 μg. Vitamin B12, equivalent to 1 U.S.P. Oral Unit. Previously untreated Pernicious Anaemia will usually give a full response to a daily dosage of one Biopar Forte Tablet for a 14-day period.

Samples and literature will be supplied on request.

BIOPAR FORTE TABLETS

THE ARMOUR LABORATORIES
(Armour & Company Ltd.)
Hampden Park
Eastbourne, Sussex

Telephone: Hampden Park, 740.
Grams: 'Armolab' Eastbourne.

But there are other ways—

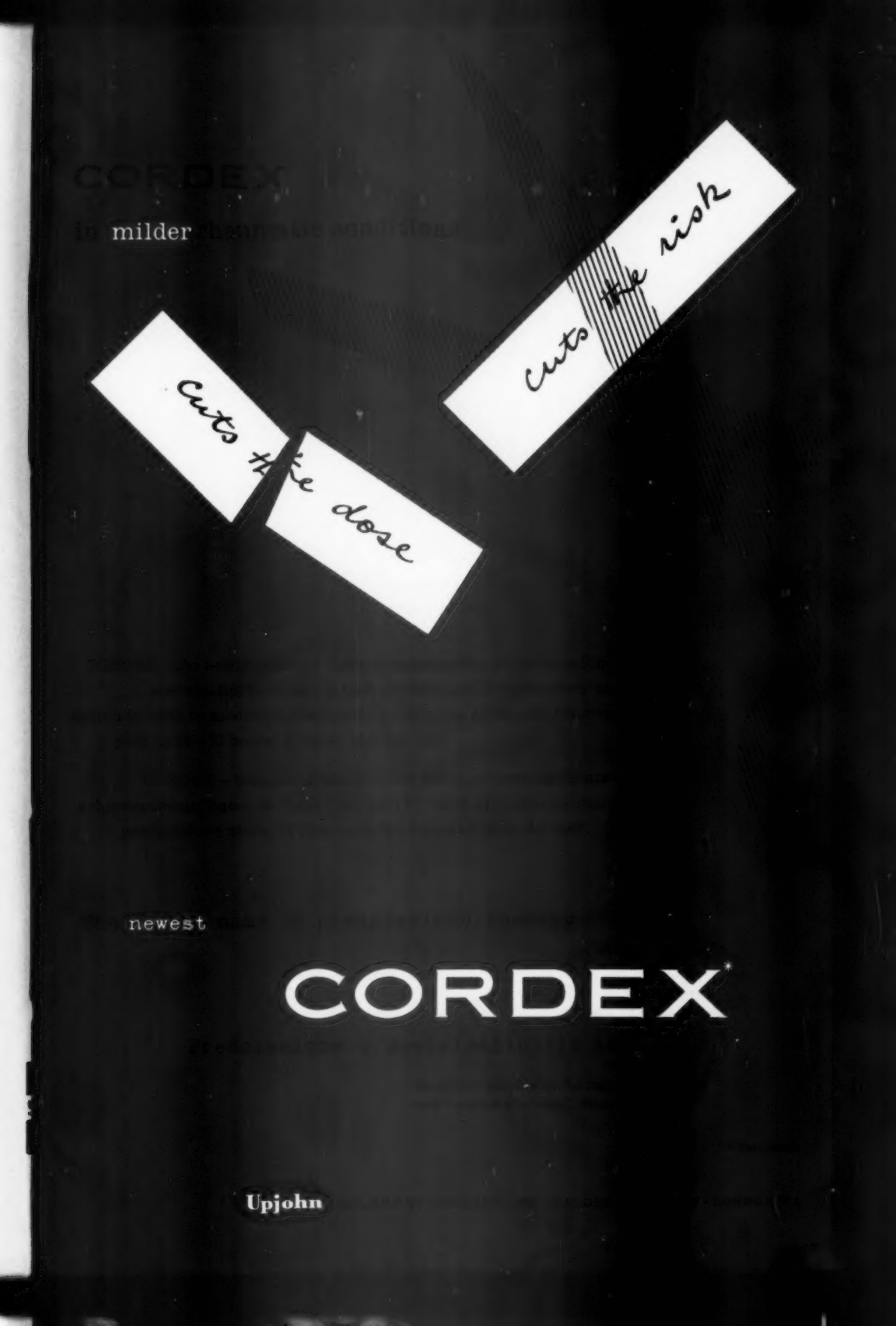
in dealing with seborrhoea capitis

Simple seborrhoea can be brought under control by the weekly use of Genisol, applied in the manner of a shampoo. Genisol has been formulated to remove the loose scales, at the same time stimulating the production of normal tissue: the inclusion of hexachlorophene prevents aggravation of the condition by bacterial invasion.

Persistent seborrhoea capitis quickly responds to the combined treatment of Genisol-Sebigen. Sebigen should be rubbed into the scalp twice daily through numerous partings in the hair, followed by frequent applications of Genisol as directed.

Genisol and Sebigen *Prescribable on E.C.10*

Genatosan Limited, Loughborough, Leicestershire.


milder
cuts the risk
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newest
CORDEX
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3 essentials to sound clinical IRON replacement

In post-haemorrhagic states; as a therapeutic or precautionary measure during and after pregnancy; in adolescents, old people and those of unsound dietary habits, Ferraplex B is ideal for iron-deficiency anaemias of all kinds.

1 It contains adequate FERROUS iron in a form yielding rapidly increased and sustained haemoglobin levels.

2 The supplements it contains—copper, complete vitamin B complex, ascorbic acid—ensure that not only the additional iron but that present in the diet is fully utilised for haemopoiesis.

3 It is extremely well tolerated by patients of all ages, even those who usually react unfavourably to unmodified doses of iron salts.

COMPOSITION

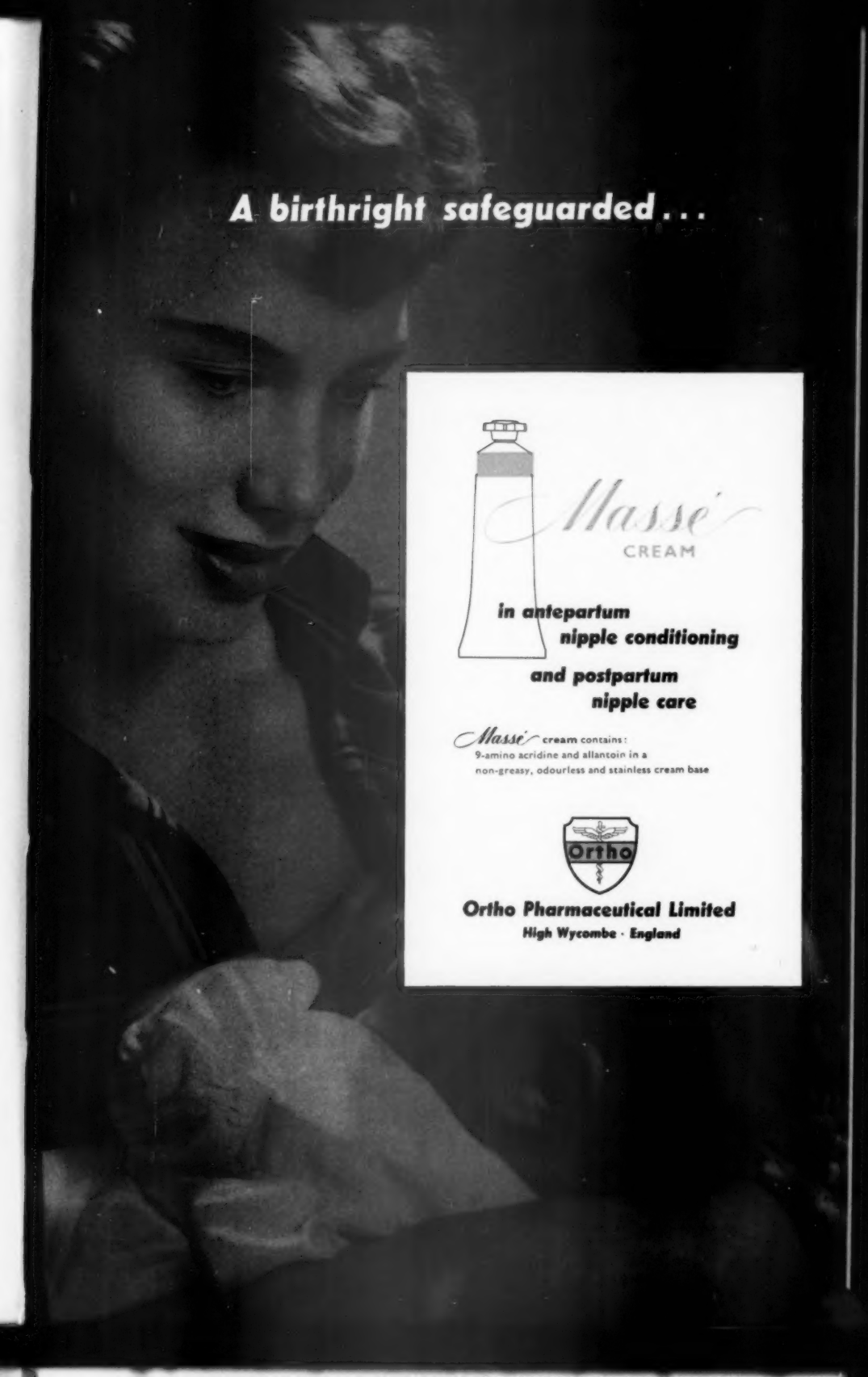
Average daily dose of six FERRAPLEX B tablets contains:

FERRI SULPH. EXSICC., B.P. . . . . 1 gramme
COPPER CARBONATE . . . . . 2 mg.
ASCORBIC ACID (Vitamin C) . . . . . 50 mg.
VITAMIN B COMPLEX EXTRACT: 2 grammes *prepared from brewers' yeast and including*
Aneurine hydrochloride (Vitamin B_1) . . 3 mg.
Riboflavine (Vitamin B_2) . . . . . 6 mg.
Nicotinamide . . . . . 30 mg.
and all the other naturally occurring factors of the vitamin B complex.

Bottles of 50 tablets: 5/3d *(Retail); 250 tablets* 15/6d *(Basic N.H.S. price).*

BENCARD **FERRAPLEX B**

C. L. BENCARD LTD · PARK ROYAL · LONDON · N.W.10


A birthright safeguarded . . .
Massé
CREAM
in antepartum
nipple conditioning
and postpartum
nipple care
Massé cream contains:
9-amino acridine and allantoin in a
non-greasy, odourless and stainless cream base
Ortho
Ortho Pharmaceutical Limited
High Wycombe · England

For safe, efficient *hydrocortisone* treatment of upper respiratory tract disorders

VASOCORT SPRAYPAK

intranasal hydrocortisone and two decongestants to reduce inflammation and oedema in

acute, chronic and allergic rhinitis

sinusitis

and nasopharyngitis

'Vasocort Spraypak' contains hydrocortisone alcohol 0.02% and two decongestants: phenylephrine hydrochloride 0.125% and 'Paredrinex' (p-hydroxyamphetamine hydrobromide) 0.5%. Because 'Vasocort' contains such low concentrations of hydrocortisone, phenylephrine and 'Paredrinex' it seldom produces untoward reactions.
It is an ideal preparation for use in children.

Smith Kline & French
represented by Menley & James, Limited

VO.PA37 (col)

INTRODUCING

sterisil VAGINAL GEL

TRADE MARK

Active against all the common pathogenic organisms of the vagina including Trichomonas, Monilia and Haemophilus Vaginalis, the organism responsible for the so-called "non-specific" infections.

Needs fewer applications and a shorter period of treatment.

Odourless.

Non-toxic.

Non-staining.

PRESENTATION
Sterisil is available in tubes sufficient for six applications and six disposable applicators are supplied in the same pack.

DOSAGE
Sterisil is effective for the treatment of all vaginal infections. It is recommended that a course of 12 applications be followed, even though a clinical cure may be achieved after six.

sterisil
VAGINAL GEL

WILLIAM R. WARNER & CO. LTD.

STER 347/7

PREDNISONE and PREDNISOLONE
Now Available

The release of products containing Prednisone and Prednisolone for prescription by General Medical Practitioners on form E.C.10 has been announced by the Ministry of Health.

'DELTACORTONE'
(PREDNISONE) Trade Mark

'CODELCORTONE'
(PREDNISOLONE) Trade Mark

'DELTACORTONE' and 'CODELCORTONE' are indicated in rheumatic diseases, collagen diseases, bronchial asthma—and in similar conditions where adrenal hormonal therapy is indicated. Average maintenance dose ranges from 5 mg. to 20 mg. daily.

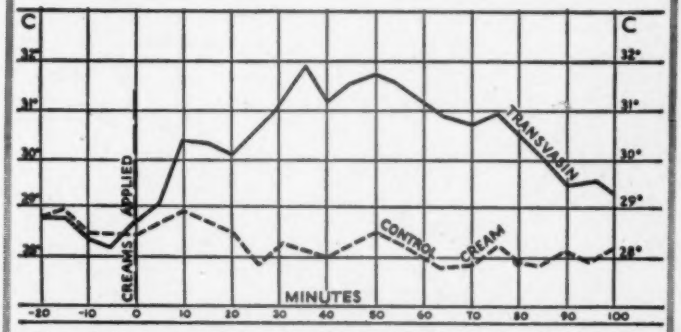
Prednisone and Prednisolone, the delta analogues of Cortisone and Hydrocortisone, produce anti-inflammatory, anti-rheumatic and anti-allergic effects similar to those of Cortisone and Hydrocortisone but with considerably lower dosage. Evidence suggests that sodium retention and potassium excretion are not so pronounced with the recommended doses of 'DELTACORTONE' and 'CODELCORTONE' as with the higher doses of Cortisone and Hydrocortisone necessary for an adequate therapeutic response.

'DELTACORTONE' and 'CODELCORTONE' are supplied as 5 mg. tablets in bottles of 30, 100 and 500.

MSD

MERCK SHARP & DOHME LIMITED, HODDESDON, HERTS.

An experiment to show the effect of Transvasin on skin temperature



The graph above is of an experiment to measure the effect of Transvasin on skin temperature on a subject. The solid line plots the skin temperature before and at intervals after a single application of one inch of cream (0.924 grams) from a tube of Transvasin. The broken line gives similar information with regard to the application of a plain vanishing cream used as a control. Skin temperatures were measured with an electro-thermo couple every five minutes for two hours.

IT IS generally agreed that cases of soft-tissue rheumatism and of many types of arthritis benefit by hyperaemia of the affected tissues. Transvasin, which contains two quick-acting esters of nicotinic acid, induces such a deep and prolonged hyperaemia at the same time as it produces superficial erythema.

In addition to the esters of nicotinic acid, Transvasin contains the fat- and water-soluble esters of salicylic and p-aminobenzoic acids. Both these well-tried analgesic drugs are readily conveyed through the skin in therapeutic quantities and enable an effective concentration to be built up where they are needed.

Transvasin is now being widely prescribed, with successful clinical results. Since a very small quantity is sufficient for each application, the cost of treatment is extremely low.

COMPOSITION

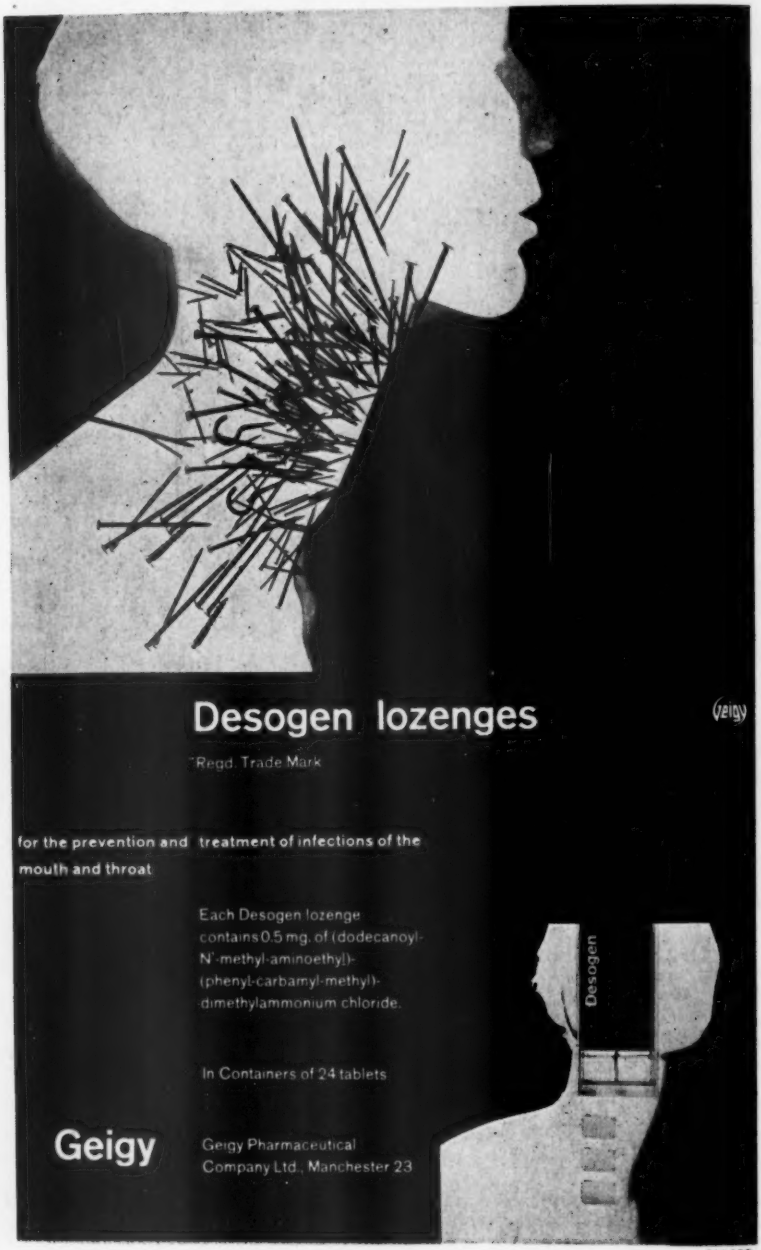
Salicylic acid tetrahydrofur-furyl-ester	14%
Nicotinic acid ethyl-ester	2%
Nicotinic acid n-hexyl-ester	2%
p-Aminobenzoic acid ethylester	2%
Water-miscible base ad ...	100%

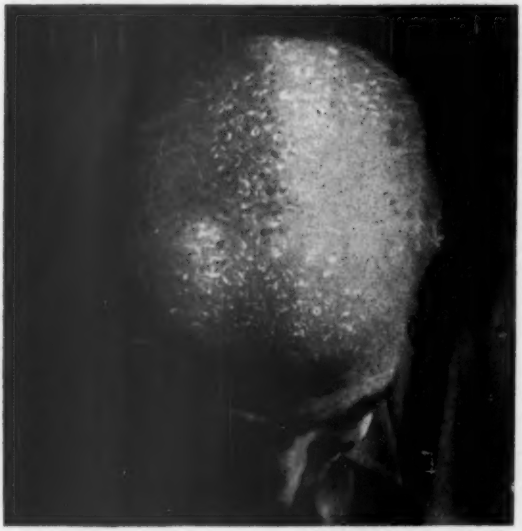
Transvasin is available in 1 oz. tubes, basic N.H.S. price of 2/6 + Purchase Tax, and is not advertised to the public. Samples and literature will be gladly sent on application.

Transvasin

LLOYD-HAMOL LTD., 11 WATERLOO PLACE, LONDON, S.W.1. WHItehall 8654/5/6

'Transvasin' is a registered trade mark of Lloyd-Hamol Limited


Desogen lozenges
Geigy
®Regd. Trade Mark
for the prevention and treatment of infections of the mouth and throat
Each Desogen lozenge contains 0.5 mg. of (dodecanoyl-N'-methyl-aminoethyl)-(phenyl-carbamyl-methyl)-dimethylammonium chloride.
In Containers of 24 tablets
Geigy
Geigy Pharmaceutical Company Ltd., Manchester 23
Desogen
PH.108a



SEBORRHOEIC DERMATITIS

PRAGMATAR

highly effective in a wide range of skin disorders

a versatile and safe preparation containing tried and proved agents for the treatment of *seborrhoeic dermatitis* (including *cradle cap*), *eczematous eruptions*, *psoriasis*, *fungous infections* and *dandruff*

Pragmatar — cetyl alcohol-coal-tar distillate, sulphur and salicylic acid

Smith Kline & French

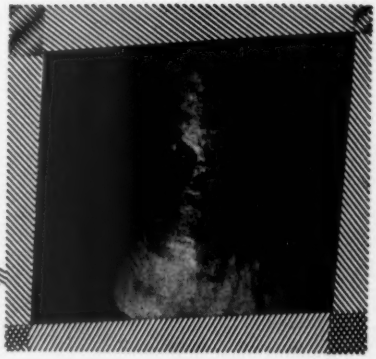
represented by Menley & James, Limited, London

'Pragmatar' is a registered trade mark

PR:PA27

The use of stabilized Trypsin

A NEW TREATMENT FOR **ULCERS** **ABRASIONS** **BURNS** **PYODERMIAS**



ANY MEDICAL PRACTITIONER knows how stubbornly resistant to any therapy a long-standing varicose ulcer can be. The reason is partly the diminished blood supply, but more perhaps the formation of a pus-containing layer and of crusts which cover the ulcer and impede the healing process. Similar difficulties are often encountered in the treatment of wounds and abrasions.

PROTEOLYTIC ACTION

It has long been known that the proteolytic enzyme Trypsin could digest crusts by the process of physiological currettage. The difficulty has been to incorporate the trypsin in a stable preparation. In Biotrase trypsin remains active physiologically for over one year. A certificate of stability has been issued by a leading Institute of Bio-chemistry. It rapidly dissolves crusts and scabs and leaves a clean, granulating surface.

Biotrase has been designed by Lloyd-Hamol of London and Zurich for the treatment of infected skin lesions. Apart from trypsin, it contains two new antiseptic agents of proved bacteriolytic properties, Ca-N-Hydroxymethylglutaminate and 2,2¹ thiobis-(4,6-dichlorophenol) designated bithionol, both of which are effective against a wide range of gram-positive and gram-negative pathogenic organisms and do not cause skin sensitivity. Biotrase also contains Carbamide, included for its buffering properties.

INDICATIONS FOR USE

Biotrase may be used wherever there is an infected—or potentially infected—breach of surface of the skin. Common conditions for its use include the following: Varicose, diabetic and post-thrombotic ulcers; wounds, and second and third degree burns; infected and necrotic skin conditions, including pyodermias; boils and carbuncles (following incision).

COMPOSITION OF BIOTRASE

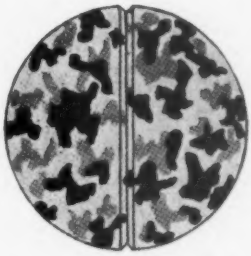
Trypsin pur.	0.16%
Ca-N-Hydroxymethylglutaminate	5.00%
2,2¹ thiobis-(4,6-dichlorophenol)	0.50%
Carbamide B.P.	5.00%
In polyethylene glycol	

Biotrase

Biotrase is available in 35g. tubes at a basic N.H.S. price of 3/9d. plus Purchase Tax. Samples and literature are available to medical practitioners on request.

'Biotrase' is a registered trade mark of
LLOYD-HAMOL LIMITED
11 Waterloo Place, London, S.W.1.

Belladenal



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(Each tablet contains: 0.25 mg: L-alkaloids of belladonna and 50 mg. phenobarbitone)

Gradual liberation of the active principles provides sustained action for about 10 hours

One tablet morning and evening ensures round-the-clock action

Samples will be gladly supplied upon request

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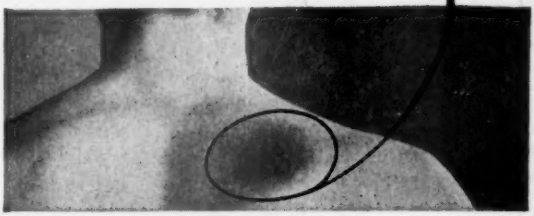
Rubriment relieves pain in such conditions as muscular rheumatism, fibrositis, strains and sprains.

Some minutes after application the skin becomes flushed and there is a comforting feeling of warmth which persists for many hours.



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A new long-acting rubefacient—safe and effective

RUBRIMENT contains a new substance, the benzyl ester of nicotinic acid, which gives a long-lasting rubefacient effect. Experimental studies have shown that even after prolonged and repeated application no damage or irritation to the skin structure was caused.

Ten minutes after application there is a feeling of warmth and the area becomes flushed. This redness is due to the dilation of the small cutaneous blood-vessels. Clinical reports have been received of the efficacy of Rubriment for relief in such conditions as muscular rheumatism, lumbago, fibrositis, strains and sprains. The immediate and prolonged vasodilatory action of Rubriment also provides relief for unbroken chilblains.

Available in two forms Rubriment (2.5% nicotinic acid benzyl ester and 0.1% Capsicin) is available either as a cream or as a liniment, both of which are non-greasy.

The cream is rapidly absorbed and needs only gentle application. It is supplied in tubes of 20 g. (approx.). Basic price to N.H.S., 2/2d.

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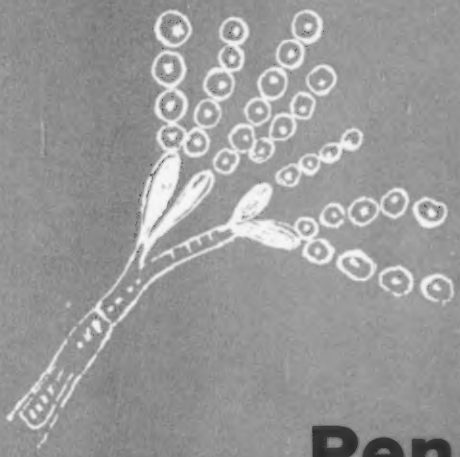
Directions for use One application per day has been found to be effective for the majority of patients, though a fresh application may be made, if necessary, at more frequent intervals. ***Rubriment is not advertised to the public and can be prescribed on E.C.10.***

RUBRIMENT Horlicks Limited

PHARMACEUTICAL DIVISION SLOUGH BUCKINGHAMSHIRE



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(BENZATHINE PENICILLIN)

the reliable, oral antibiotic

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PACKS

Suspension in bottles of 60 c.c.
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(complete with dropper)

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For many people, however, life is played to a continuous accompaniment on the drums. It is in these tense, anxious patients that Equanil has proved so outstandingly successful. Equanil restores repose safely, reliably and effectively, enabling such patients to get back into the swing of a normal life.

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He could not be enjoying himself more. But tomorrow he is going into hospital. There's nothing seriously wrong with him, but the time has come when he must put his trust in doctors and nurses. And they, in their turn, put their faith in BRITISH OXYGEN equipment and gases. In thousands of cases, every day, BRITISH OXYGEN equipment and gases are used to ease pain and to save lives.

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Especially with children and old people. No side-effects

Unrelated to morphine derivatives or guaiacol and with none of their disadvantages, Becantyl suppresses useless cough. The active ingredient in Becantyl is Sodium-2: 6-ditertiarybutylnaphthalene monosulphonate. This chemical, which does not cause constipation, anorexia, drowsiness or other side-effects, is the result of original research.

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Adults: 2 teaspoonfuls

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three times a day or as prescribed.

Becantyl has no B.P. or N.F. equivalent, is not advertised to the public, and may be prescribed on form E.C.10.

BECANTYL

Literature and Samples available from the Medical Information Department
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treatment for ear infection

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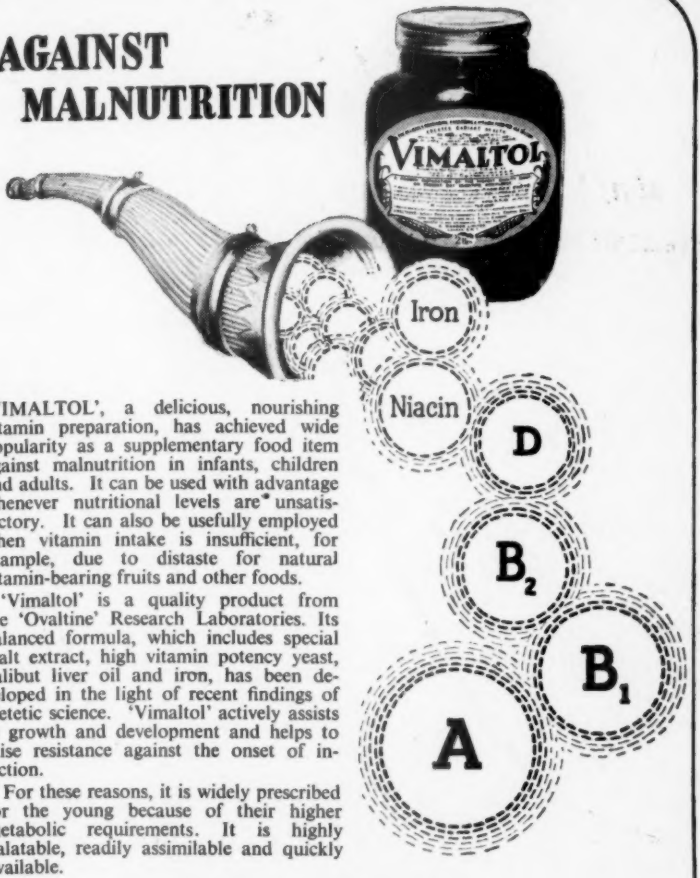
AGAINST MALNUTRITION



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'Vimaltol' is a quality product from the 'Ovaltine' Research Laboratories. Its balanced formula, which includes special malt extract, high vitamin potency yeast, halibut liver oil and iron, has been developed in the light of recent findings of dietetic science. 'Vimaltol' actively assists in growth and development and helps to raise resistance against the onset of infection.

For these reasons, it is widely prescribed for the young because of their higher metabolic requirements. It is highly palatable, readily assimilable and quickly available.

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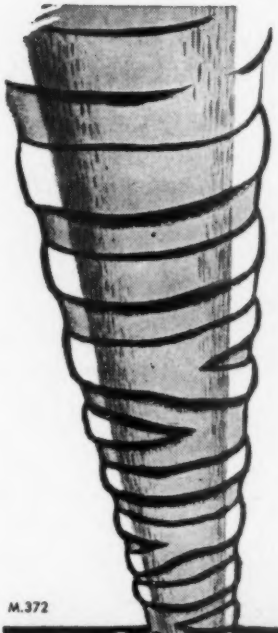

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'Asmac' Tablets combine in a single prescription 'official' drugs recognized for their reliability to effect mental sedation, decongestion, expectoration and bronchodilatation.

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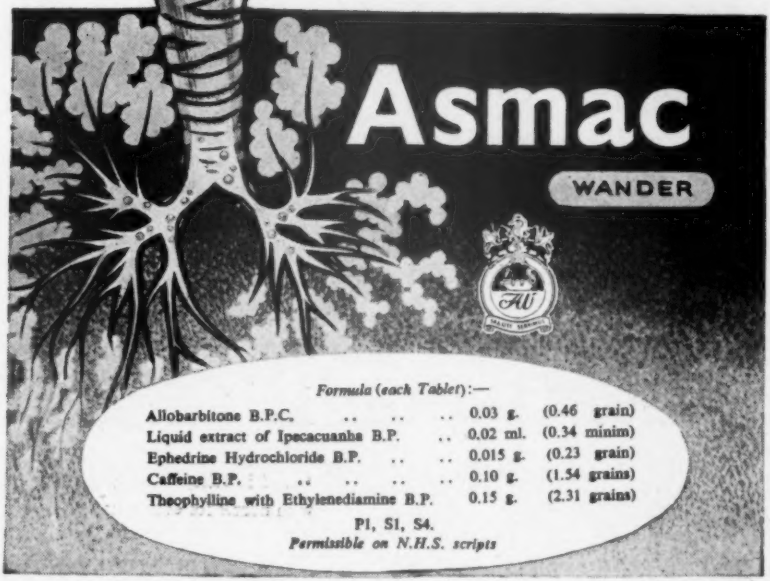

Formula (each Tablet):—

Allobarbitone B.P.C.	0.03 g.	(0.46 grain)
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Permissible on N.H.S. scripts

Beats the lot

'CORTISPORIN' kills the bacteria of surface infections

This new ointment contains bacitracin, neomycin and polymyxin B sulphate. It has a wider range of activity than any single antibiotic, destroying gram-positive and gram-negative organisms, including *Ps. pyocyanea, proteus* and staphylococci. Bacterial resistance or skin sensitisation are unlikely with 'Cortisporin'; nor does it induce cross-resistance or cross-sensitisation to penicillin or other antibiotics. It often succeeds where other antibiotics fail. 'Cortisporin', by virtue of its other constituent, hydrocortisone, also reduces inflammation.

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Active Principles:
Acetylsalicylic acid 250 mg. Phenacetin 250mg. Codeine phosph. 10mg

Dose:
1 or 2 tablets, 2 or 3 times a day, depending on the severity of the pain.

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THE PRACTITIONER

No. 1064 FEBRUARY 1957 Volume 178

THE MONTH

The Symposium

Our symposium on 'Diseases of the blood' this month illustrates both the advances which have been made in the understanding and management of this important group of diseases and also how much still requires to be done before they are brought fully under control. Pernicious anæmia and the anæmias of pregnancy are now completely under control, but primary thrombocytopenic purpura still presents difficulties. Acute leukæmia and hæmophilia are probably the two most dreaded of the blood dyscrasias, but in both progress is being made. Particularly in hæmophilia, much can now be done to make life more bearable for the unfortunate victims. The symposium concludes with an authoritative review of 'Hæmoglobin and its abnormalities' which brings together and interprets a mass of highly technical reports on the subject. Hitherto, most of this information has been lost to the clinician in the more specialized journals. Dr. Lehmann's article is a long one but it provides the first detailed review of the subject specially written for the clinician. The intensive study of hæmoglobin which has been going on during the last decade has not only provided clues to the solution of many hæmatological problems, it has opened up many new promising lines of research in anthropology as well as clinical medicine. The clinician has always to remember, as Dr. Cathie points out in his article on 'Anæmia in infancy and childhood', that 'when a subject is developing so rapidly, today's laboratory wonder is tomorrow's routine clinical practice'.

Conscription for Nurses?

It is becoming increasingly difficult to be ill at home. Not because of any shortage, or inadequacy, of family doctors, but simply because there is no-one to nurse the patient in his own home. The result is threefold. An unnecessary number of patients have to be admitted to hospital, thus involving the National Health Service in unnecessary expense. The family doctor is unable to maintain the high standards to which he aspires because many of his 'interesting cases' are removed outwith his control. The sick citizen is deprived of his right of being nursed at home—among those 'things', to quote an experienced family doctor (J. H. Hunt: *The Practitioner*, 1956, **177**, 312), 'that make our homes more desirable to live in than a hotel, and being ill at home often more pleasant than being ill in hospital'. Although

the problem applies to all age-groups, it is probably most urgent in the case of the elderly. Indeed, according to Dr. R. L. Kitching, in his article on 'The home nursing service' (p. 234), 'the present neglect of the aged sick is as disgraceful as the callous disregard for the safety of children on the roads'. He might well have quoted in support of his statement the following pathetic example reported in a recent issue of the 'News Letter' of the Distressed Gentlefolk's Aid Association:—

> 'An old lady who had once been a governess, lived all alone in rooms in a large town. She had always kept a diary. One day she was found dead, and in her room there were only a bed and a chair. On the chair beside her was this diary, and on every page below the date there was the single pathetic entry, "Nobody came" '.

Dr. Kitching has three suggestions for dealing with the present crisis. The first is that we should do more to recruit part-time nurses for the home nursing service. The second is that, pending an increase in the supply of State-enrolled assistant nurses (S.E.A.N.), whose training takes about two years, there should be established a new service of part-time 'district assistant nurses', with a much shorter training. The third is that nurses should be conscripted for nursing. This last suggestion will raise howls of protest from many quarters, but it is evidence of the acuteness of the emergency that such a suggestion should even be made. The mere idea will be anathema to many, but what other solution have the nursing authorities, local authorities and Ministry of Health to offer to Dr. Kitching and his fellow-practitioners throughout the country, when they say that they 'cannot go on any longer waiting for volunteers while old people are suffering as they have not suffered for a hundred years'? Deeds, not words, are required in an emergency such as this. As a contribution towards easing the situation, perhaps the Minister of Health will bring to the attention of his opposite number in the Ministry of Labour the concluding paragraph of his Deputy Chief Medical Officer's article in our recent symposium on 'Home Care and Nursing (*The Practitioner*, 1956, **177**, 9). If our womenfolk were encouraged to stay at home, rather than rush into factories and offices, the need for home nurses would be considerably reduced.

Placeboes

EVERY clinician worth his salt has his favourite placebo. Paradoxically, as H. Keith Fischer and B. M. Dlin (*Amer. J. med. Sci.*, 1956, **323**, 504) point out, in an interesting study of placebo therapy, 'the subject receives scant notice in textbooks of treatment and is often ignored in lectures and courses in therapeutics'. The paradox, of course, is easily explained, as textbooks of treatment are either written by pharmacologists with no clinical experience, or, if written by clinicians, have to concentrate upon the use of the growing number of potent preparations now at the disposal of the clinician. Perhaps the most convincing demonstration of the value of placeboes has come from the statisticians with

their insistence upon the use of 'controls' in all clinical trials of new drugs. Over and over again, these trials have shown considerable, if not complete, recovery in many of the patients receiving the placebo, or 'control', preparation.

It may, of course, be argued that this recovery was the natural course of the disease and that the placebo had nothing to do with it, but there still remains a not inconsiderable number of patients in whom the discriminate use of a placebo facilitates the process of recovery by convincing the patient during the recovery stage that something is being done to help him. Fischer and Dlin write as psychiatrists but express the view that 'placebo therapy should not be discarded in general practice. It only needs to be put in its place'. They emphasize two important practical points for the successful use of placeboes. One is that the patient should not be aware that he is receiving a placebo. The second is that the placebo should contain some active constitutent, and not be merely a sugar-coated excipient. They refer to patients in their investigation who became suspicous that they were receiving a placebo and tried to find out what was in the pill or tablet they were receiving. This, of course, is a well-recognized hazard of placebo therapy, and in the past was often overcome by including some bitter in the prescribed mixture or pill. Many practitioners now include a small amount of a sedative in the placebo pill. Placebo therapy will never be a substitute for a full history and understanding of the patient's troubles but, used with discrimination, it will often play a useful part in tiding the patient over a period of stress or through some psychosomatic disturbance.

Silence for the Cardiologist

'COMMONLY encountered levels of background noise can and do seriously impair the physician's ability to hear murmurs through the conventional stethoscope'. This may sound platitudinous to many, but there are probably few clinicians who appreciate to what extent such background noise may interfere with the detection of heart murmurs. Dale Groom (*Amer. Heart J.*, 1956, **52,** 781) has investigated the problem in the hospitals attached to the Medical College of South Carolina, and his findings are of more than passing interest to all clinicians. Preliminary investigations showed that the background noise levels ranged from 100 decibels in the hospital boiler room down to 55 decibels in the medical clinic examining room. In the heart clinic office it was 69 decibels, compared with 68 decibels in the library. The significance of these figures may be appreciated from a comparison with figures for inside a DC-6 airliner and for a house in the country, which are 105 and 30 decibels respectively.

The actual investigation was carried out in a sound-proofed room in which the background noise level was 35 decibels. Forty members of the faculty staff served as subjects in the experiment, in which conditions simulating actual stethoscopic examination were reproduced. Without

exception, everyone tested required an increase in intensity of the murmur for it to be perceived when the background noise level was raised from that of the sound-proof room to that of the ordinary examining room. The average increase for the 40 subjects was 11.8 decibels. In other words, 'the same murmur which could be heard in the quiet room had to be increased to more than twelve times the intensity to be detected under conditions encountered in hospital wards and examining rooms'. An interesting finding was that the cardiologists required the greatest increase in intensity of the murmur when the background noise level was raised (18.5 decibels), whereas the pathologists and other non-clinicians required the least (8 decibels). 'If this is what happens in hospitals which are supposedly quiet places, how many early murmurs are missed when examinations are carried out in schools, what our American friends call 'military induction centres', and factories?

Eunuchs and the Gout

'EUNUCHS do not take gout or become bald, a woman does not take gout unless her menses be stopped, a young man does not take gout unless he indulges in coition'. This quotation from Hippocrates is one of the many apt allusions to the association between gout, sex and drink referred to by G. D. Kersley in a delightful little essay on the folklore of gout (*Medical Journal of The South-West*, 1956, **71(iv)**, 136). Like so much folklore it tends to make the best of both worlds, on the one hand associating the disease with sex and drink, and on the other with learning. Warner, for instance, described gout as 'dominus morborum et morbus dominorum'—freely translated by Kersley as 'the disease of the erudite and the greatest of all diseases'. As Kersley points out, the association with leadership and learning is amply typified by Harvey, Linnæus, Newton, the two Pitts and Fox, and that wisest of all clinicians, Thomas Sydenham, once said that 'gout rarely attacks fools'.

The association with 'high living and low thinking' is equally well documented in the folklorian files, and is supported by A. B. Garrod who dated gout back to the time when man first indulged in luxury. In his fifteenth-century essay on gout, Williams Cadogan gives as the background of gout: 'If I am not mistaken the laudible qualities, which are at present the most in fashion, are keeping mistresses, debauching friends' wives, cheating at the gaming tables and at Newmarket, indulging in every excess and refinement in eating and drinking and speaking in Parliament'. Goethe is quoted as saying that to beguile the tedium of spa treatment he always engaged in some new love affair. Many seventeenth-century victims of the disease must have appreciated Sydenham's sage advice: 'Drink wine, have gout—drink no wine, and have the gout', adding: 'I count water by itself crude and injurious'. The passing of gout may be a sign of the times, but its folklore is a rich source of perennial interest to the student of human nature.

THE DIAGNOSIS AND TREATMENT OF PERNICIOUS ANÆMIA

By E. K. BLACKBURN, M.D., F.R.F.P.S.

Consultant Hæmatologist, The Royal Infirmary and Hospital, Sheffield

ADDISONIAN pernicious anæmia is a chronic disease occurring most commonly in white persons in temperate climates between the ages of 40 and 70. Occasional cases are seen, however, even under the age of 30. The anæmia is of megalocytic, normochromic type associated with a megaloblastic bone marrow due to deficiency of cyanocobalamin (vitamin B_{12}), which has been shown recently to have the following empirical formula: $C_{63}H_{90}O_{14}N_{14}PCo$. Cyanocobalamin is the extrinsic factor of Castle, and liver contains a cyanocobalamin-like hæmopoietic principle which is effective in the treatment of pernicious anæmia and subacute combined degeneration of the spinal cord. Absorption of cyanocobalamin is defective in pernicious anæmia due to inadequate gastric secretion of the intrinsic factor of Castle, which is an enzyme separate from the pepsin or rennin normally secreted by the glands of the upper part of the stomach. Degenerative changes in the peripheral nerves and in the central nervous system often accompany the anæmia.

Abnormality of other links in the chain of absorption, storage and utilization of the hæmopoietic principle may precipitate a similar anæmia. For example, the principle may be absent from the diet, intestinal disease may prevent its absorption and liver disease its storage, whilst gastrectomy or carcinoma of the stomach may cause failure of supply of intrinsic factor. Such anæmias should not be styled pernicious. Diagnosis should be made only after careful consideration of the clinical and laboratory findings.

CLINICAL PICTURE

The onset of the disease is usually insidious, and the patient typically feels relatively well with a relatively severe degree of anæmia. The hair is often prematurely grey and early symptoms include lack of energy, slight breathlessness on exertion, headache, dizziness, anorexia, sore tongue, nausea, flatulence, abdominal pain, diarrhœa, and peripheral paræsthesiæ.

As the disease advances pallor develops. Earlier diagnosis has diminished the frequency of the classical lemon-yellow jaundice, but irregular melanotic pigmentation of the face, neck, abdomen, forearms and hands may also occur. The early symptoms gradually progress, and palpitations, precordial pain, œdema of the ankles and sacrum, cardiomegaly, low blood pressure, hæmic systolic bruits, vomiting and epigastric pain and tenderness often develop. Loss of weight is common, but may be completely absent. Pyrexia unrelated to infection, and albuminuria are often seen in severer

cases. Dysphagia and koilonychia are rare. The spleen is occasionally palpable.

Peripheral neuritis causes the peripheral paræsthesiæ, a common early symptom. Later, loss of vibration sense and of sense of position are found, and spastic ataxia or, more rarely, flaccid paraplegia may develop. 'Glove and stocking' impairment of all forms of sensation may be present in the limbs. Lightning pains, gastric crises and girdle pains may occur. Whilst paralysis of the sphincters is a late manifestation, sexual power is lost early. These neurological signs of subacute combined degeneration of the spinal cord may be found with little or no accompanying anæmia, but abnormalities of the bone marrow such as megaloblasts, megaloid cells and macrogranulocytes are usually present. Rarely, herpes, optic atrophy, papillœdema, cranial nerve palsies and speech disturbances are found.

Mental symptoms, which develop in a few cases, range from minor disturbances of memory to confusion, disorientation, delusions and hallucinations. Electroencephalographic changes are common, even in those cases of pernicious anæmia with no cerebral symptoms (Samson, Swisher, Christian and Engel, 1952).

Amenorrhœa is common, but hæmorrhagic symptoms are rare. The commonest sites of the latter are probably the retinæ and the ears.

In severer cases diagnosis usually presents little difficulty. The patient is relatively well as compared with the degree of anæmia, although general symptoms of the latter are present. These, along with a sore tongue, peripheral paræsthesiæ and gastro-intestinal upset, suggest the clinical diagnosis. In early cases, however, there may be only one or two symptoms such as persistent diarrhœa or soreness of the tongue. Primary disease of the alimentary, cardiovascular or nervous systems may be closely simulated. It is important to diagnose cases before the spinal cord is affected.

The family history is often helpful because there is often a history of gastric achlorhydria, achlorhydric hypochromic anæmia, pernicious anæmia or subacute combined degeneration of the cord in blood relatives.

Infections of the urinary tract and cholecystitis are common, and myxœdema occasionally complicates the picture. The incidence of carcinoma of the stomach in pernicious anæmia is probably at least three times as high as in the rest of the population.

LABORATORY FINDINGS

The clinical diagnosis should always be confirmed, or otherwise, by the following laboratory investigations.

Peripheral blood.—In early cases the hæmoglobin and red cell levels may be within the normal range. There is, however, usually increased variation in size (anisocytosis) and in shape (poikilocytosis) of the red cells with a tendency towards megalocytosis (large mature cells derived from megaloblasts in the bone marrow). Hypersegmented polymorphonuclear cells are often seen.

In severe untreated cases there is diminution in hæmoglobin, red cells, leucocytes, and platelets. There is marked anisocytosis and poikilocytosis of the erythrocytes which are larger than normal and fully hæmoglobinized. Increase in polychromatic and stippled cells and in reticulocytes and siderocytes may be found. Occasionally megaloblasts are seen; they are nucleated red cells most easily detectable in smears from the buffy layer of the hæmatocrit. The colour index (C.I.) and mean corpuscular volume (M.C.V.) are increased. The total leucocyte count is diminished in more advanced cases due to a fall in granulocytes which are large and multisegmented. Platelets are also reduced, and hypoprothrombinæmia may occur (Warner and Owen, 1942). The serum bilirubin is often increased.

Bone marrow.—The predominant nucleated red cells are megaloblasts; giant granulocytes and multisegmented polymorphs are seen, and the platelet precursors called megakaryocytes may be normal, diminished or increased in number. The latter show increased segmentation and degenerative changes.

Gastric juice analysis.—A histamine-fast achlorhydria is almost invariably found.

The bone-marrow examination clinches the diagnosis of a megaloblastic state in untreated cases. Most difficulty is then found in excluding other causes of such a condition. Although accompanying iron deficiency may occasionally complicate cases of pernicious anæmia, it should stimulate careful search for primary alimentary tract disease such as carcinoma of the stomach or steatorrhœa.

The peripheral blood and bone marrow findings in *carcinoma of the stomach* may be indistinguishable from those of pernicious anæmia. Furthermore, the anæmia may respond to cyanocobalamin therapy. Usually, however, there is marked loss of weight, a sallow complexion, occult blood in the stools, a rise in the corrected erythrocyte sedimentation rate and sometimes a leucocytosis. A barium meal and/or gastroscopic examination are usually diagnostic, but occasionally laparotomy is the final court of appeal. Rarely, gastric leiomyomas result in all the above findings.

A megaloblastic anæmia occasionally follows *gastrectomy*, more commonly after the total or subtotal than the partial operation, and usually after a period of at least two years. It usually responds to cyanocobalamin therapy, but occasionally folic acid is needed for an optimum response (Welbourn, Nelson and Zacharias, 1956). A similar anæmia rarely follows intestinal resection and short-circuit operations, intestinal strictures and blind loops.

Steatorrhœa is often associated with a megaloblastic anæmia, but there is usually less anisocytosis and poikilocytosis of the red cells, and the M.C.V. and red cell diameter may even be within the normal range. The features of tropical sprue are a history of residence abroad, fatty stools, and absence of nervous complications; free hydrochloric acid is usually present in the gastric juice. Apart from the residential qualification, similar remarks apply to cœliac disease and idiopathic steatorrhœa. These two diseases are often

associated with a long history of changes in fat and calcium metabolism.

There is usually free hydrochloric acid in the gastric juice in the *pernicious anæmia of pregnancy*. Less anisocytosis and poikilocytosis are found in the peripheral blood than in pernicious anæmia, and the mean red cell diameter and M.C.V. may be normal. The anæmia usually responds well to folic acid, but occasional cases need cyanocobalamin and/or proteolysed liver. The causative factors cease to operate in the lactational period.

Hepatic cirrhosis rarely causes a megaloblastic anæmia, but there are usually obvious signs of hepatic disease, and free hydrochloric acid is often found in the gastric juice.

Megaloblasts are sometimes seen in *acute leukæmia*, but the bone-marrow smears are diagnostic. *Acquired hæmolytic anæmia* may be partly megaloblastic or megaloid, but the spherocytosis, reticulocytosis, increased red cell fragility and presence of abnormal hæmagglutinins are some of the differential features. Megaloblastosis rarely occurs in *scurvy* and responds to ascorbic acid therapy. The rare *megaloblastic anæmias of childhood* are sometimes associated with ascorbic acid deficiency, and are not of pernicious type. They rarely respond to cyanocobalamin therapy, and folic acid is always effective.

Following Badenoch's (1954) report, a relatively small number of cases of megaloblastic anæmia developing in *epileptic patients undergoing anticonvulsive therapy* have been reported. There is usually free hydrochloric acid in the gastric juice, and the fat balance test is normal, thus ruling out steatorrhœa. Our experience, and that of others, has shown that these cases respond to folic acid therapy, and occasionally to cyanocobalamin.

A rare form of megaloblastic anæmia in this country is associated with fish-tapeworm (*Diphyllobothrium latum*) infection. There is often free hydrochloric acid in the gastric juice, and the worm or parts of it may be seen on examination of the stools, but the central nervous system may be affected just as in pernicious anæmia. The anæmia responds to elimination of the worm or to cyanocobalamin therapy.

Cases of Hodgkin's disease, lymphosarcoma, splenic anæmia, infective endocarditis and syphilis are associated occasionally with a macrocytic anæmia. Careful clinical examination and scrutiny of bone-marrow smears rule out pernicious anæmia.

SPECIAL TESTS

During recent years a number of new methods have been devised for the differentiation between the two main groups of megaloblastic anæmia: those due to cyanocobalamin deficiency and those due to folic acid deficiency. Unfortunately these techniques are unsuitable for routine laboratory use, and can only be performed in specially equipped centres. They have, however, added considerably to our knowledge, and include the following.

Biopsy of gastric mucosa.—When a histamine-fast achlorhydria is present, a sample of fundal mucosa obtained by gastric biopsy, if normal, excludes

pernicious anæmia. If, however, atrophy of the pernicious-anæmia type is present, the patient may or may not be suffering from the disease (Wood, Doig, Motteram and Hughes, 1949).

Use of radioactive cyanocobalamin.—In effect this is a test for the presence of intrinsic factor. The absorption of cyanocobalamin is assessed by measuring the radioactivity in the fæces after an oral dose of cyanocobalamin labelled with Co^{60}. Callender, Turnbull and Wakisaka (1954) found that 31 per cent. of the radioactivity in the test dose was recovered from the fæces in the normal person, compared with 88.7 per cent. in cases of pernicious anæmia. The percentage of the test dose recovered is greatly reduced in pernicious anæmia if sources of intrinsic factor are given with the radioactive cyanocobalamin. It is, however, unsafe to assume that a patient who excretes a large amount of the test dose has pernicious anæmia. Thus, for example, this may occur after gastrectomy in the absence of any anæmia.

Serum cyanocobalamin levels.—The serum cyanocobalamin level may be measured by biological assay. The organism most suitable for measuring low serum levels is probably *Euglena gracilis*. Whilst mean normal values exceed 300 millimicrograms per ml., values below 100 millimicrograms per ml. are found in patients with megaloblastic anæmia due to cyanocobalamin deficiency (Mollin and Ross, 1953a, 1953b; Spray, 1955). In megaloblastic anæmias due to folic acid deficiency the serum cyanocobalamin levels are normal. This method has been of particular value in the diagnosis of clinically doubtful subacute combined degeneration of the cord associated with minimal hæmatological changes.

Folic-acid excretion test.—Girdwood's (1953) folic-acid excretion test estimates the urinary output of folic acid after subcutaneous and oral doses of 5 mg. of synthetic folic (pteroylglutamic) acid. Difficulties in interpretation have arisen, and these are admirably reviewed by Girdwood (1956). Thus, for example, a low urinary output of folic acid may follow a test dose when there is primary cyanocobalamin deficiency. On the other hand, a normal urinary output may be found when the patient's tissues are depleted of folic acid: e.g. in pernicious anæmia of pregnancy.

Amino-aciduria.—Using the method of urinary chromatography, excess amino-aciduria has been found in Addisonian pernicious anæmia and not in other megaloblastic anæmias (Keeley and Politzer, 1956). This technique may prove very valuable in the future.

Other techniques such as the inhibition of maturation of megaloblasts in marrow culture by plasma from cases of pernicious anæmia (Lajtha, 1950), and chemical assays of cyanocobalamin levels (Fantes and Ireland, 1950) are of great academic interest, but are unlikely to become routine diagnostic tests.

TREATMENT

A firm diagnosis should be made before specific treatment is begun, because partial therapy obscures the typical bone-marrow picture. As pernicious anæmia is a deficiency disease, replacement therapy must be continued

throughout life. This treatment should ensure maximum reversion towards normal health in the shortest possible time. Thereafter the patient should have no symptoms attributable to the disease.

INITIAL TREATMENT

The severely anæmic patient should remain in bed until the erythrocyte count has risen to at least 3 millions per c.mm. With spinal cord complications, mobility within reason should be encouraged at a lower erythrocyte level because this type of disability is exaggerated by prolonged immobilization in bed.

Diet is not of much immediate importance, but should be liberal, well-balanced, and contain factors assisting blood regeneration, such as meat, eggs, fresh fruit and green vegetables.

Blood transfusion, which does not interfere with bone-marrow diagnosis, is rarely needed. Indications for this therapy include the presence or imminence of heart failure, mental disturbance due to cerebral anoxæmia, the imperative need for surgery, and the presence of a complication such as severe infection which is likely to interfere with the therapeutic response. The serious risk of circulatory overloading is minimized by giving packed red cells at a rate not exceeding 1 ml. per kg. body weight per hour, and by not giving more than 1000 ml. per transfusion.

SPECIFIC THERAPY

At the outset the patient should understand that treatment will be necessary for life, but that otherwise he will be a normal person. Effective preparations for replacement therapy in this deficiency disease are many.

Cyanocobalamin (*vitamin* B_{12}) given intramuscularly is, in my opinion, the treatment of choice at present (Blackburn, Burke, Roseman, and Wayne, 1952). One satisfactory schedule consists of 100 micrograms (μg.) weekly or fortnightly in uncomplicated cases until the blood is normal and symptoms have disappeared. As, however, the tissues of normal persons probably contain 1000 to 2000 μg. of cyanocobalamin, and those of cases of pernicious anæmia little or none (Girdwood, 1952), it is probably desirable to restore the tissue reserves by giving five injections, each of 1000 μg. of the vitamin, during the first few weeks in the initial phases (Mollin and Ross, 1953b). Much cyanocobalamin is lost in the urine, but about 200 to 300 μg. from each injection is retained. Thereafter, 100 μg. every two weeks gives an ample margin of safety, except in cases with neurological involvement, when this dose should be given weekly for at least six months. Double or treble these doses should be given if intercurrent infection supervenes.

The serum iron level falls within forty-eight hours of the first injection (Hawkins, 1955) and the bone marrow becomes normoblastic after seventy-two hours. Reticulocytosis begins on the second or third day and subsides to normal by the fourteenth day. Regular blood examinations at least every

three months should be made during the maintenance period, the closest clinical and hæmatological control being still essential.

As compared with liver extracts, cyanocobalamin injections are small in bulk, constant in potency, relatively cheap, and in general do not lead to sensitization phenomena and control the disease more efficiently (Blackburn *et al.*, 1952). Very rarely, general and local reactions of an allergic nature, which cease after desensitization, are encountered.

Cyanocobalamin by *nasal insufflation* (Israëls and Shubert, 1954) is a useful form of therapy if intramuscular injection is not desired. It is not suitable for patients with nasal obstruction or chronic catarrh and is relatively cheap.

Various *oral preparations containing cyanocobalamin and intrinsic factor* are available. Such therapy at present does not appear to be as reliable as cyanocobalamin injections, and it is more expensive (Blackburn, Cohen and Wilson, 1955). Further trials in this field are desirable, and are being carried out. Oral cyanocobalamin alone is effective in some circumstances, but is not recommended for routine management (Chalmers and Hall, 1954).

Crude liver extracts have no place in the therapy of the average case, whilst *refined liver extracts* are often fortified with cyanocobalamin, and therapeutic dosage varies with the product.

Some patients find that *proteolysed liver* and *desiccated hog's stomach* have a relatively unpleasant taste. Furthermore, they are much more expensive than parenteral cyanocobalamin. If cyanocobalamin therapy is refused, the usual dose of proteolysed liver is one teaspoonful twice or thrice daily, and that of hog's stomach one to three tablespoonfuls daily.

Folic acid therapy is normally contraindicated, because it does not control, and may precipitate, nervous degeneration. Furthermore, the hæmoglobin and red cell levels are not always maintained after a satisfactory initial response.

Blunderbuss therapy with mixtures of iron, folic acid, liver extract, desiccated stomach and cyanocobalamin is to be severely avoided for many reasons. Thus, for example, it obscures the diagnostic value of the blood and bone-marrow examinations without preventing many signs and symptoms such as subacute combined degeneration of the cord, and it is uneconomical.

ADJUVANT THERAPY

Iron should be given in full doses if such an additional deficiency is present at the outset or if it develops later during maintenance therapy.

Physiotherapy is important in cases with neurological involvement. Passive movements, massage, and dry heat improve the muscular and circulatory tone and also the feeling of well-being. Coordination exercises should be instituted as early as possible.

PROGNOSIS

With proper and adequate therapy the prognosis is generally excellent.

Regular clinical review, with hæmoglobin and erythrocyte estimations, are desirable every three to six months. Neurological signs and symptoms diminish for the first six months, after which little improvement takes place. The shorter the duration of neurological symptoms prior to specific therapy, the better the prognosis. Larger numbers of these cases are now reaching ripe old age. Hence the diseases associated with this state occur with increasing frequency.

FAILURE OF RESPONSE TO PROPER TREATMENT

This may occur at the outset or during maintenance therapy. It usually implies: (1) incorrect diagnosis, (2) inadequate and/or too infrequent dosage, (3) sepsis, infection or other complication such as malignant disease. Occasionally, however, cases fulfil the ordinary diagnostic criteria for pernicious anæmia, without evidence of steatorrhœa, hepatic disease, or other known causes of megaloblastic anæmia, and yet fail to respond to either parenteral cyanocobalamin or to purified liver extract. Some of these cases respond to proteolysed liver or to folic acid therapy.

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THE LEUKÆMIAS

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THERE is evidence that the incidence of leukæmia is slowly increasing and there must be few general practitioners who in the course of a year's work do not find themselves faced with difficult and distressing problems connected with this disease. In the past decade much interest has been focused on many aspects of research on leukæmia and hopes have been raised regarding the possibilities of treatment by new chemotherapeutic agents. It is the purpose of this article to present for the family doctor a brief survey of the current outlook on the disease with particular reference to the question of treatment.

NATURAL HISTORY OF LEUKÆMIA

Leukæmia is a condition characterized by an abnormal and excessive proliferation of leucopoietic tissues throughout the body, usually associated with an increase in the total number of circulating leucocytes and with immature forms in the peripheral blood. The cause of the disease remains unknown but it is commonly accepted as a neoplastic process because of the uncontrolled proliferation of cells which involves organs other than the bone marrow and lymphatic glands. On the other hand, as the cells show no truly invasive properties and the disease appears to start simultaneously throughout the leucopoietic tissues, there are features which suggest that the cause of the condition may lie in a generalized metabolic or humoral disturbance affecting the growth of leucocyte precursors. There is no convincing evidence that in man the disease is either transmissible or inherited. Whilst leukæmia is an invariably fatal condition, terminating by reason of progressive anæmia, hæmorrhage or intercurrent infection, the course of the disorder varies considerably in different age-groups and according to whether the proliferative process affects the granulocyte, lymphocyte or monocyte series in an acute or chronic form. It is most important to remember the natural history of the disease in assessing the prognosis and need for treatment in any particular case. In childhood the condition is nearly always acute, running a rapidly progressive course with a fatal outcome in a matter of weeks. Most cases in the early years are of the acute lymphatic variety. In the elderly, chronic lymphatic leukæmia is the commonest type with a rate of progress that is often so slow that it need not materially affect the normal expectation of life. It seems that in such cases the lymph glands and spleen are mainly involved in the initial stages and the very gradual replacement of the bone marrow by proliferating lymphocytes means that anæmia, granulopenia and thrombocytopenia develop

only after a considerable time and until then the patient remains in relatively good health. In this group of patients it is worth remembering also that the leukæmia may be of the aleukæmic variety in which the total white cell count in the peripheral blood is not increased. These cases are liable to be treated unsuccessfully for a slowly progressive anæmia before the diagnosis of chronic aleukæmic lymphatic leukæmia is established by examination of the bone marrow.

It is only against the background of the variations in the natural history of leukæmia that a rational approach to the problems and benefits of treatment can be undertaken.

ACUTE LEUKÆMIA

In any age-group acute leukæmia may occur and the diagnosis should be considered in patients presenting with fever, general malaise and a rapidly advancing anæmia. Because of thrombocytopenia, hæmorrhagic manifestations are common and the reduction in normal polymorphonuclear leucocytes often results in ulcerative infective lesions in the mouth and throat. Many patients with acute leukæmia are first referred to the ear, nose and throat department of a hospital. The benign condition of infectious mononucleosis is probably the most important differential diagnosis of acute leukæmia in children and young adults. Once the diagnosis of acute leukæmia is established by blood examination, the determination of the actual cell type involved is often a point of mainly hæmatological interest, for, whilst temporary improvement can be hoped for with treatment in a proportion of children with the lymphatic variety, the ultimate outlook in all cases is uniformly grave and, in many, attempts at treatment seem merely to prolong or aggravate the misery.

CHRONIC LEUKÆMIA

Chronic myeloid, and chronic lymphatic, leukæmia are diseases that occur mainly after middle-age, the lymphatic type being the more common and affecting elderly males more than females. Both conditions are insidious in onset and it is a matter of speculation as to how long abnormal blood changes have been developing before clinical manifestations appear that lead to the diagnosis first being made. This is probably especially true in chronic lymphatic leukæmia where a slowly rising lymphatic count and slight lymph-gland and splenic enlargement may be the only findings in an otherwise healthy elderly patient. In chronic myeloid leukæmia it is commonly the presence of an enlarged and painful spleen that draws attention to the condition. In this variety bone-marrow replacement occurs earlier than in the lymphatic type and results in anæmia, bone pain and other manifestations that lead to blood examination. Once the diagnosis is established it is commonly held that the expectation of life is two to three years in chronic myeloid leukæmia, and three to five years in chronic lymphatic leukæmia although some patients live longer in both disorders, and especially in the

latter. It seems surprising that in general the results of treatment appear to do little to prolong the natural course of the disease, although a great deal can be done to keep the patients in a state of health in which they can lead a normal and useful life until the proliferative process no longer responds to palliative measures. In most cases the terminal stage develops quite rapidly, as an acute acceleration of the disorder takes place with a dramatic change towards immaturity in the leucocyte precursors in the marrow and peripheral blood. Many cases first diagnosed as acute leukæmia are in fact in the terminal acute phase of a chronic form of the disease which has gone unnoticed for a considerable time.

TREATMENT OF ACUTE LEUKÆMIA

It is as well for the practitioner faced with the problem of dealing with a case of acute leukæmia to inform the relatives from the outset that in this condition the outlook is uniformly bad, that there is no known cure, and that only symptomatic or palliative treatment can be offered. The gravity of the illness will become only too rapidly apparent in the so-called fulminating cases with high fever, sepsis, profound anæmia and a generalized bleeding tendency. In these patients, and especially in those in whom the condition represents the terminal phase of chronic leukæmia, it is extremely doubtful if even the most heroic therapeutic measures are likely to prove of the slightest beneficial effect. The correct treatment is almost certainly to provide symptomatic comfort and to let nature take its course. In other cases, when the patient is less severely ill when first diagnosed, there is more time to consider the trial of chemotherapeutic agents in the hope of inducing a temporary remission. Some clinicians, however, hesitate to use these drugs on the moral grounds that at best they can only postpone the fatal outcome and any temporary response may add to the anguish of relatives hoping for a cure.

Accumulated experience with chemotherapy in recent years has shown that remissions can be induced in about half of the cases of acute lymphatic leukæmia in children, with prolongation of survival time from a few weeks up to periods approaching two years. In the other varieties of acute leukæmia and in cases in adults, the results are much less encouraging, with remissions both fewer and of shorter duration. Nevertheless, it would seem correct and advisable to attempt some such treatment in all but the very worst cases as there is always the chance that the patient may be kept alive until some more effective remedy is introduced. Furthermore, it is only by the trial of chemotherapeutic agents that knowledge in this field can be extended. It is generally agreed that radiotherapy has no place in the treatment of acute leukæmia and is in fact contraindicated.

The drugs that have attracted much interest in recent years are known as anti-metabolites because it is believed that they act by depriving rapidly dividing leukæmic cells of factors essential in nucleic acid metabolism. The folic-acid antagonists were first tried in 1948 after it had been found that

the administration of folic acid could greatly accelerate the proliferative process of acute leukæmia. In this connexion it must be emphasized that folic acid should never be given to any patient suffering from any variety of leukæmia.

'*Aminopterin*' (4-amino-pteroylglutamic acid) is the best known and most potent member of the folic-acid antagonists and is a most dangerously toxic drug capable of producing profound depression of bone-marrow function and marked ulceration of the buccal and alimentary tract mucosa. Given in doses of 0.5 to 1 mg. daily to children suffering from acute lymphatic leukæmia, however, it has been shown repeatedly to produce partial or complete remissions of the disease in about one-half of the cases. Remission usually occurs within two to five weeks, with the bone marrow being rendered hypoplastic before more normal hæmopoiesis returns. Toxic effects are common and often of such severity that dosage has to be modified or discontinued, and many clinicians are hesitant to use 'aminopterin' because they feel that the treatment is almost worse than the disease. In spite of this, many reports are available of remarkable remissions induced by the drug and children have been restored to apparent full health for periods of several months before inevitable relapse has occurred. Adult patients respond much less often, with remissions occurring in only about 10 per cent. of cases. Once remission has been obtained, reduced 'aminopterin' dosage should be carried on in continuous or interrupted maintenance treatment, the control of which demands frequent observation of the state of the peripheral blood and bone marrow. Relapses often respond to the reinstitution of full dosage and in many cases two or more remissions can be induced before the disease process becomes resistant to further treatment.

6-*mercaptopurine* is another anti-metabolite, acting as a purine antagonist, and the results of its first trial in human leukæmia were reported in 1953. It has the great advantage over 'aminopterin' in causing no toxic side-effects in the alimentary tract, but like 'aminopterin' it can produce serious hæmopoietic depression so that the most careful hæmatological control is essential in the regulation of dosage. This is usually 2.5 mg. per kg. body weight given daily, and about two to three weeks' treatment is required before any remission becomes evident. Subsequent maintenance therapy is needed, with the dosage adjusted according to the clinical progress. The results in collected series indicate that 6-mercaptopurine can induce single or several remissions in about 60 per cent. of cases of acute lymphatic leukæmia in children and in a few adults. It seems to be the only drug of any value in acute monocytic leukæmia, which has long been the variety most notably resistant to therapy. Whilst 6-mercaptopurine has largely replaced 'aminopterin' as the chemotherapeutic agent of choice in acute leukæmia, the latter still remains a valuable alternative drug which, by reason of its different mode of action, may be effective when the disease proves resistant to the purine antagonist.

Cortisone and *corticotrophin* may also induce dramatic temporary improve-

ment in acute lymphatic leukæmia. The incidence of remission is somewhat less in children and more in adults than with 'aminopterin' and 6-mercaptopurine, and the remissions are usually of shorter duration. As the beneficial effect is usually seen much earlier than with the chemotherapeutic drugs, many workers advocate concurrent hormone and anti-metabolite therapy from the outset. Cortisone acetate is given orally in a dosage of 300 mg. daily for adults, or 100 to 200 mg. daily for children, and continued for ten to fourteen days. Alternatively, prednisone can be given by mouth in one-fifth of the above dosage. Cortisone seems particularly valuable in patients with hæmorrhagic manifestations due to thrombocytopenia and in those with marked agranulocytosis. In the latter, antibiotics are also often required to combat associated intercurrent infection. Hormone therapy appears of no value in acute monocytic leukæmia except perhaps to help reduce a bleeding tendency while 6-mercaptopurine is being tried. The treatment of acute myeloid leukæmia is most unsatisfactory with any form of therapy at present available.

In the treatment of acute leukæmia *blood transfusion* plays an important part in correcting the anæmia and helping to control blood loss during the period before a response to chemotherapy or hormone therapy can be expected. Few clinicians now advocate the heroic measures sometimes attempted by exchange transfusion. There can be no doubt, however, of the striking improvement that in some cases can follow the transfusion of fresh whole blood, and many workers have regarded this as indicating the replacement or restoration of humoral factors that have become deranged in the causation of the leukæmic process.

TREATMENT OF CHRONIC LEUKÆMIA

Bearing in mind the natural history of the chronic leukæmias, it is obvious that it is the patient rather than the disease who should be treated. For as long as the clinical state remains satisfactory, no attempt should be made to embark on radiotherapy or chemotherapy when the only abnormal finding is a raised white blood cell count in the peripheral blood. In chronic myeloid leukæmia, advancing anæmia, loss of weight and the presence of a grossly enlarged and often painful spleen are manifestations which demand treatment. In chronic lymphatic leukæmia marked enlargement of lymph glands and spleen, weight loss and developing anæmia likewise indicate the need for therapy. In contrast to the position in acute leukæmia treatment in the chronic cases can usually offer a real improvement in the general health of the patient who may be enabled to lead an active existence for two to three years and often for considerably longer.

Radiotherapy remains the best method of treatment in both chronic forms of leukæmia and is given by the wide field (body bath) technique or to the spleen alone. The dosage is controlled by frequent blood counts, with particular attention to the need to avoid undue depression of the platelet count. *Radioactive phosphorus* given intravenously is an alternative method

of producing irradiation effects, but is not widely used in Britain.

When radiotherapy is not available, treatment by *chemotherapeutic drugs* can prove effective especially in chronic myeloid leukæmia. *Busulphan* ('myleran') is a preparation allied to the nitrogen mustard group of compounds, with an action on dividing cells similar to that of irradiation. Given orally in a dose of 1 to 4 mg. daily, it can induce satisfactory clinical and hæmatological remission in a high proportion of cases. 6-*mercaptopurine* has also been found to give encouraging results in this condition. Chemotherapy is less satisfactory in chronic lymphatic leukæmia although triethylenemelamine (tetramine; 'TEM') can produce benefit in some cases. It is a nitrogen mustard derivative given orally in a dosage of 2.5 to 10 mg. weekly, but is particularly liable to cause irreversible bone-marrow depression and its administration requires most careful hæmatological control.

It will be some time before a statistical comparison can be made of the relative merits of the chemotherapeutic agents and radiotherapy, but there is a growing tendency for clinicians to employ the drugs and they certainly represent a great advance in areas where patients are unable to obtain radiotherapy.

CONCLUSION

The general practitioner has a most important part to play in the management of a patient with leukæmia. Whilst much of the specialized treatment with radiotherapy or chemotherapy demands initial and follow-up care in hospital departments equipped to deal with complicated techniques, it is to the family doctor that the patient and his relatives will turn for everyday advice and help. By giving symptomatic treatment in the most difficult cases of the acute form of the disease, and by keeping a careful watch for the need for further measures in the chronic leukæmias, the practitioner holds a key position in the team of workers so necessary for the optimum handling of the patient. He will be expected to know the whys and wherefores of the measures being employed and will be questioned about reports of new treatments that attract attention in the lay press. It is up to the hospital staff to keep the family doctor fully in the picture by giving him all details of the treatment plan, especially when the newer chemotherapeutic agents are being tried. All of these drugs are capable of doing far more harm than good by producing severe hæmopoietic depression and so the closest liaison between the hospital and the practitioner is essential for their correct administration.

Whilst there is as yet no cure for leukæmia the fact that within recent years drugs are available which can influence the disease, represents progress of fundamental importance. Their discovery has stimulated the most intensive research into the biochemical processes concerned with the growth of normal, leukæmic and neoplastic cells, and encourages the hope that far greater therapeutic advances in this field may not be long delayed.

ANÆMIA IN PREGNANCY

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In Britain today anæmia still remains common in all walks of life despite the fact that most forms are preventable or curable. French (1955) stated that in general practice he saw 80 patients a year with iron-deficiency anæmia—about 1.6 per cent. of all his patients—and that in half of these the anæmia was associated with pregnancy.

CAUSATION

By reducing efficiency (Reimann, 1956), anæmia of any severity interferes with a mother's ability to look after her home and her children. Measures to reduce the incidence are therefore of importance. Surveys have shown that repeated pregnancies play a considerable part in the causation of maternal anæmia (Davidson *et al.*, 1935). Post-partum hæmorrhage is undoubtedly important, but so are the physiological demands of pregnancy, particularly in regard to iron metabolism.

In health the mature woman on an adequate diet ingests between 15 and 20 milligrams of iron a day, but the 'iron barrier' of the intestinal wall limits the absorption to the amount necessary to meet the iron losses from the body. These losses in the urine, in desquamated epithelial cells and through menstruation, amount to about 2 milligrams a day. In addition, there is within the body a closed circuit iron exchange with a turnover of about ten times this amount. Most of this iron comes from the breakdown of effete red cells and goes into the formation of hæmoglobin for new red cells with a small amount for the enzyme systems of new cells in other tissues.

The balance in these exchanges is maintained and buffered by the tissue stores amounting to as much as 1 gramme of iron, a reserve sufficient to provide hæmoglobin for two-fifths of the circulating red cells or, if iron absorption ceased, to keep up the supply of red cells for over a year. If the fine balance is disturbed and the woman's iron losses exceed her uptake, the stores dwindle and vanish, the hæmoglobin level becomes unstable and finally she sinks into iron-deficiency anæmia. It would appear that a considerable proportion of women have difficulty in maintaining the balance and probably more than half have an inadequate iron store.

In pregnancy, and particularly after the twentieth week, the physiological demands for iron increase. The fœtus requires up to 500 milligrams while the normal expansion of the mother's blood volume, including the placental circulation, estimated at over 20 per cent., requires a similar amount. This is partly offset by conserving some 25 milligrams of iron a month through the cessation of menstrual losses and the remainder is provided by a small increase in iron absorption and by drawing upon the stores. In many women

these demands cannot be met adequately during pregnancy. The cherished belief, that this is due, in part at least, to a reduction in the gastric secretion of hydrochloric acid interfering with iron absorption, has recently been questioned (Clark and Tankel, 1954). In addition, many pregnant women have poor appetites whilst others undoubtedly have an inadequate diet. Losses of blood from such sources as nose bleeding, gastro-intestinal ulceration and hæmorrhoids, so prominent in the causation of iron-deficiency anæmia at other times, are of little importance in the anæmia of pregnancy.

Similar difficulties affect the supply of other hæmatinic factors which cannot be synthesized in the body, e.g. cyanocobalamin and folic acid; it may well be that pregnancy strains the production of certain specific amino-acids. In many pregnant women, too, the degree of utilization of the various hæmatinics appears to be diminished and either higher dosage is required or the response is slower.

CLASSIFICATION

When anæmia is found in pregnant women it may either be an integral part of the pregnancy or may be an accidental association. The anæmias of pregnancy can thus be divided into:—

The intrinsic anæmias of pregnancy.—(1) Iron-deficiency anæmia. (2) Megaloblastic anæmia. (3) Refractory anæmia. (4) Hæmolytic anæmia.

The anæmias associated with pregnancy.—(5) Pre-existing iron-deficiency anæmia. (6) Anæmia of toxic and infective states. (7) Pernicious anæmia. (6) Chronic hæmolytic anæmia. (9) Anæmia of other hæmatological disorders.

Iron-deficiency anæmias (1 and 5) are common, megaloblastic and refractory anæmias account for under three per cent. of cases and the other varieties are rarities and together form only a fraction of one per cent. The problem of anæmia in pregnancy is thus mainly the problem of iron-deficiency.

IRON-DEFICIENCY ANÆMIA

Iron-deficiency anæmia occurs in a considerable proportion of pregnant women. Lillie, Gattenby and Moore (1954) estimated that in Dublin over 23.8 per cent. of the pregnant women had a hæmoglobin level below 10 grammes per 100 millilitres (67 per cent. Haldane), whilst at another hospital in the same city Doyle and McGrath (1954) put the figure even higher at 31.4 per cent. Scott and Govan (1949), in Glasgow, found 20.1 per cent. below 9 grammes (60 per cent. Haldane), and Holly (1955) in the United States stated that without treatment only 21.8 per cent. of women maintain their early pregnancy hæmoglobin level, 54.8 per cent. show a moderate degree of iron-deficiency, and 23.6 per cent. a severe degree. Roughly, a quarter of the women attending the antenatal clinic at King's College Hospital have a hæmoglobin level below 12 grammes (80 per cent. Haldane) at or before the 32nd week.

The pre-existing variety of iron-deficiency anæmia is usually seen early in pregnancy and may become very severe. It will be present at the first visit at

12 to 16 weeks, when the iron demands of pregnancy should still be amply covered by the arrest of menstruation. It is usually detectable clinically but, if missed, progresses steadily and may be life endangering during labour. A large proportion of the severe cases discovered in the women attending the antenatal clinic are of this variety. In this hospital during the last four years some 1.5 per cent. of the pregnant women had a hæmoglobin level below 9 grammes (60 per cent. Haldane), more or less the same figure for the frequency of a similar degree of anæmia in all the new patients attending the hospital. Whilst there are many different factors making up these figures the agreement may be taken as support for the belief that most of the severe cases were incidental to, although no doubt exaggerated by, pregnancy.

In these cases the peripheral blood is of the usual hypochromic microcytic type and the marrow is moderately active, micronormoblastic, shows complete absence of iron stores (fig. 1) and perhaps also some distortion of leucopoiesis with giant metamyelocyte formation.

The intrinsic iron-deficiency anæmia of pregnancy is not present before 20 weeks, but develops in the subsequent months as the demands grow to increase the mother's red cell mass and meet the fœtal requirements. Partly as a result of the nature of the upset, a withdrawal of iron inhibiting the marrow without the stimulation of rapid blood loss, and partly because when detected the hæmoglobin has rarely had time to fall below 9 grammes, the customary hypochromic peripheral blood picture is not developed and the red cells, although small, have a fairly normal hæmoglobin content.

Whilst severe anæmia is usually, although by no means always clinically, obvious, lesser degrees are notoriously difficult to judge. There may be some breathlessness, tiredness, ankle œdema and loss of appetite, but that is all. The sore tongue, the cracked mouth angles and koilonychia commonly associated with iron-deficiency anæmia are missing, for these develop slowly and, if present, are evidence that the anæmia is one of considerable standing which is complicating pregnancy.

The idea of a 'physiological anæmia of pregnancy', often used as a cloak for indifference to this cause of maternal morbidity, has lost much of its support. Over half the women in this area maintain a normal hæmoglobin level throughout pregnancy without treatment; there are definite microcytic changes in the red cells; and the majority of those who become anæmic can be restored to normal hæmoglobin levels by treatment (Davis and Jennison, 1954). Most of the advocates have shown that the plasma volume increases out of proportion to the red cell mass, but have not excluded the possibility that they are merely demonstrating in another way what we already know—that anæmia is common in pregnancy. I believe that the normal woman on an adequate diet does not show any anæmia during pregnancy. It has been argued that a slight degree of anæmia may be an advantage during labour, but this hardly fits the facts. The majority of women from better homes show no fall in hæmoglobin and do very well

in the puerperium and those women who are found to have a mild degree of anæmia, still above the 'physiological hæmoglobin level', nearly always state that they feel better when this is corrected.

If it is beneficial to correct, so far as possible, any anæmia, some method of screening for anæmia is necessary to pick those requiring treatment. Alternatively iron, or iron, folic acid and oral vitamin B_{12} (Lowenstein

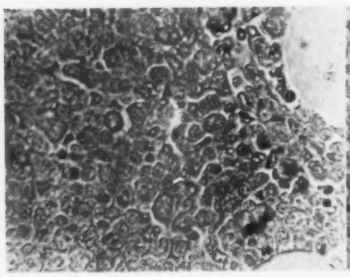

FIG. 1

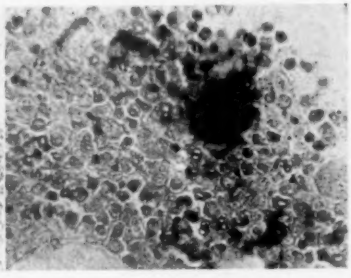

FIG. 2

FIG. 1.—The marrow in iron-deficiency anæmia—from a case of menorrhagia. No iron visible. (× 160). Stain: Prussian blue.

FIG. 2.—The same marrow after a year on oral ferrous gluconate. Despite some continuing menorrhagia the iron is now present in normal quantities (grade 2). (× 160). Stain: Prussian blue.

et al., 1955), may be given routinely. The difficulty with the routine issue of tablets is that given in this way many of the mothers, especially the multiparæ, will not take them regularly. The problem with screening is to decide the best time and the hæmoglobin level below which treatment should be instituted. Bearing in mind that the anæmia develops late in pregnancy, except in a small group of severe cases which may be suspected clinically, the thirty-second week appears to catch most of the cases and still leaves adequate time for treatment. If the hæmoglobin at this time is about 12 grammes (80 per cent. Haldane) it is unlikely to fall below 10.5 grammes (70 per cent. Haldane) in the last six weeks and, in my opinion, this is the minimum level at which a woman should be allowed to face labour. Holly (1955) and Doyle and McGrath (1954) agree that anæmia with a hæmoglobin level below 12 grammes should be treated.

The object of treatment should be to ensure that no woman goes into labour with a hæmoglobin level below 10.5 grammes (70 per cent. Haldane) and that as many as possible should be in the normal range of 13 to 15 grammes (86 to 102 per cent. Haldane). It is also advisable to see that by the end of the puerperium every woman is on the way to rebuild her store of iron in preparation for any subsequent pregnancy. Contrary to the suggestion sometimes made, these stores can be replaced by oral iron or, better still, by an adequate diet although this takes time (fig. 2).

ORAL IRON

On general principles the treatment of choice is oral iron. Ferrous gluconate, 100 milligrams (three tablets) a day, gives good responses and causes little digestive disturbance. Under 10 per cent. of women show intolerance to this preparation, in contrast to over 30 per cent. who on ferrous sulphate have trouble of sufficient severity to impede treatment. In cases of difficulty the same dose of the rather more expensive ferrous succinate may be substituted, or, if the trouble lies in swallowing tablets, liquid preparations of ferrous gluconate, giving the same dose in three teaspoonfuls a day, are available.

With this treatment, by the 35th week there should be a rise in the hæmoglobin of over 1.5 grammes (10 per cent. Haldane) or to normal levels. If this has not taken place the position should be reviewed under the following headings: (1) Is the iron being taken? (2) Is the iron being absorbed? (3) Is there complicating disease such as urinary infection? (4) Is the diagnosis of iron-deficiency correct? (5) Is there blood loss? The review should include examination of venous blood to determine the mean cell hæmoglobin concentration (M.C.H.C.) and mean cell volume (M.C.V.), but it must be realized that the diagnosis of megaloblastic anæmia of pregnancy is not usually possible without examination of the bone marrow and valuable time may be lost if this is omitted. A histological estimation of the iron content of the marrow, which indicates the state of the iron stores, is of value at this stage (Davidson and Jennison, 1952). The marrow examination is sometimes delayed for a fortnight until the next review.

If, after adequate examination, it would still seem that the failure to respond is due to poor absorption of iron, parenteral iron may be used. To prove this point really requires the aid of a well-equipped and staffed hospital laboratory; a test for iron absorption consists in estimating the serum level before and two hours after a dose of oral iron.

PARENTERAL IRON

The idea of giving iron intravenously is old, but toxicity limited the possible dose to an insignificant quantity. In the last few years this difficulty has been overcome by the use of specially prepared *iron saccharates*, and the intravenous preparations on the market have proved a great advance in cases of poor iron absorption or when gastro-intestinal disorders might be aggravated by oral iron. The technique of intravenous injection must be good, for any escape into the tissues is painful. On the first day a trial dose of 1 millilitre should be given; if there is no reaction, 2.5 millilitres are given on the second day, followed by 5 millilitres containing 100 milligrams of iron each day until the desired total dose has been reached. With care this method of treatment is very successful, but there are records of severe reactions (Librach, 1953). It seems important to draw back into the iron preparation in the syringe at least an equal quantity of blood. The mixture is then injected slowly but steadily; to encourage removal of the

iron from the site, the line of the vein is massaged immediately after.

Even more recently an *iron-dextran complex* has been introduced for intramuscular use. This is a relatively non-toxic product and larger doses may be given to most individuals without any reaction, although some may find the injection of even a small amount very painful. Usually 2 millilitres of the complex are stabbed deeply into the muscles of the upper and outer quadrant of the gluteal region or into the outer side of the thigh. If there is no local or general reaction 5 ml., containing 250 milligrams of iron, should be administered on successive days (Jennison and Ellis, 1954) or two to three times a week (Scott, 1956) until the determined dose has been given.

The total amount of parenteral iron to be given is calculated from the iron deficiency. The iron required in milligrams equals the hæmoglobin deficiency in grammes per 100 millilitres of blood, multiplied by the blood volume in hundred millilitres, multiplied by 3.4, plus 500 milligrams to create a reserve store. For practical purposes the blood volume can be taken as 50 times 100 millilitres (5 litres). Alternatively, the formula suggested by the makers may be used: Dose in milligrams equals the hæmoglobin deficit in percentage (Haldane) multiplied by the body weight in pounds, multiplied by 0.3. The total course is usually between 1000 and 1,500 milligrams, given over seven to fourteen days.

It must be remembered, however, that all injections carry risk and parenteral iron therapy does cause general reactions in addition to the local pain mentioned. With intravenous iron lumbar pain is the most common and may come on within a few minutes of the injection or be delayed several hours; although very unpleasant this passes off with rest. More serious is the acute bronchospasm which may occur and even a few deaths have been recorded with excessive dosage. Such reactions seem to have become less frequent in recent times, probably through better preparations, the practice of keeping the patient at rest for about quarter of an hour after the injection and avoiding or treating very circumspectly those patients who have allergic skin and respiratory disorders. With the intramuscular injection, despite statements to the contrary, there is often some staining of the skin which persists for over a year. If the patient is warned of this difficulty and the gluteal region used there should be no trouble. More serious complications are a generalized dermatitis, usually an exacerbation of a pre-existing dermatitis, or an acute bronchospasm, usually predisposed to by a tendency to asthma or bronchitis.

Following parenteral iron therapy there should be a reticulocyte response attended by a rise in the hæmoglobin level and packed cell volume within a fortnight. In favourable cases the hæmoglobin should rise rapidly enough to reach a normal level in the four to five weeks available before full term.

BLOOD TRANSFUSION

If there is no response by the 38th week the position must once again be reviewed. If the marrow examination has already eliminated a megalo-

blastic anæmia the question arises as to whether this is an iron-refractory anæmia (Fisher and Biggs, 1955), or the diagnosis has been wrong and one of the pre-existing types of anæmia has been overlooked. From the practical point of view a decision has to be made as to whether the hæmoglobin requires to be raised by transfusion before delivery. In general terms it can be said that if the hæmoglobin is over 10.5 grammes (70 per cent. Haldane) transfusion is unnecessary, whilst if it is under 9 grammes (60 per cent. Haldane) it is probably advisable in order to get the woman to a safe level.

MEGALOBLASTIC ANÆMIA

Only rarely does pernicious anæmia affect women young enough to bear children. Although it is therefore a very rare complication of pregnancy, it has been described (Lillie *et al.*, 1954) and the possibility must be borne in mind lest it be mistaken for the more common type of megaloblastic anæmia of pregnancy and folic acid used with disastrous consequences, the patient becoming paralysed from rapidly advancing subacute combined degeneration of the spinal cord.

In temperate climates the true megaloblastic anæmia of pregnancy is a rare condition, but it is much more common in tropical and sub-tropical countries particularly where the diet is inadequate. This type of anæmia develops with about equal frequency in the last trimester of pregnancy and in the puerperium. Despite this difference in onset the two types are regarded as part of the same disorder. The condition is due to lack of folic acid or possibly cyanocobalamin or both—materials necessary for nuclear maturation in the developing red cells. This lack results from the extra demands of the fœtus not being met through poor nutrition due to a defective diet, anorexia, or digestive upsets. Although a serious condition with a considerable mortality rate if left untreated, spontaneous recovery occurs after delivery, often with recurrence in subsequent pregnancies.

In contrast to pernicious anæmia, whilst the gastric acidity may be low (Lillie *et al.*, 1954) there is rarely achlorhydria and neurological involvement never occurs. It differs, too, from the anæmia of steatorrhœa in that the fat balance is normal.

Unfortunately there are no characteristic signs or symptoms, although I believe it is possible to suspect the condition clinically. The woman looks too ill and tired for the degree of anæmia, her face is drawn, with dull shadowed eyes and the skin has a greyish-yellow tinge, whilst on questioning she admits the lack of sleep, the tiredness, the listlessness and poor appetite her appearance suggests.

Examination of the peripheral blood is of little help except in the late stages, for the condition is masked by concomitant iron deficiency, but overlobing (senility) of the neutrophils may be taken as a warning sign. A marrow puncture will give the diagnosis and if carried out by a competent hæmatologist is little more upsetting than a venepuncture. Nevertheless, with women in the advanced stages of pregnancy it is wise to

depart from the usual procedure and to admit the patient to hospital for twelve to twenty-four hours for this and other necessary examinations.

Although cases have been treated successfully with cyanocobalamin (Lowenstein *et al.*, 1955), penicillin (Foy and Kondi, 1953) and crude liver extracts, the great majority respond to folic acid even after cyanocobalamin has failed (Lowenstein *et al.*, 1955). If the diagnosis is properly established and acid is demonstrated in the stomach, possibly by the tubeless test meal (Harkness and Durant, 1953), treatment with folic acid can be bold: 15 to 20 milligrams a day continued until recovery and then tapered off over the next month. When there is any doubt about the diagnosis, for example where there is an achlorhydria, and pernicious anæmia cannot be excluded, the hæmoglobin should be watched at lengthening intervals after the end of treatment (Davidson *et al.*, 1948).

HÆMOLYTIC ANÆMIA

A chronic hæmolytic anæmia, possibly latent as in the mildest cases of acholuric jaundice, may complicate pregnancy. Although there may be some exaggeration of the red cell breakdown, the risk of precipitating an acute attack does not appear to be great. With paroxysmal nocturnal hæmoglobinuria the patient's health may improve during pregnancy, and the possibility of transfusing red cells washed free of the plasma factor which precipitates a hæmolytic attack, has reduced the danger of a hæmolytic crisis. Acute hæmolytic anæmia can also occur during pregnancy and the recognition of the variety due to sensitivity to various drugs, including simple materials such as phenacetin, is important as stopping the drug is the specific treatment. In addition to these there appears to be an intrinsic form of hæmolytic anæmia of pregnancy. Although very rare, cases have been described by a number of authors (Lillie *et al.*, 1954). In a number the mother has gone to full term, the child survived and the hæmolysis died down in the puerperium. Other cases have terminated prematurely in stillbirths and a few have had to be terminated on account of the severity of the hæmolysis. A second hæmolytic episode in a subsequent pregnancy occurred in one of my cases and a similar event was reported recently by Craig and Turner (1955).

The patient suffering from hæmolytic anæmia may complain of abdominal pain with, perhaps, vomiting and diarrhœa. She is pale, slightly jaundiced and usually fevered. The anæmia is characterized by a marked polychromasia and, correspondingly, a reticulocyte count of over 10 per cent. and often much higher. There is nearly always a leucocytosis. The patient's serum is usually yellow and the bilirubin level can be shown to be above 3 milligrams per hundred millilitres, there is urobilinogen in the urine and the daily excretion of urobilinogen in the fæces exceeds 500 milligrams. Tests such as the red cell fragility, the acid hæmolysis test, and the direct antiglobulin (Coombs) test may be used to distinguish the types of hæmolytic anæmia (Davidson, 1951).

Treatment by transfusion, using washed cells when necessary, may be sufficient to tide the patient over the crisis but often it is only of temporary value. In serious cases cortisone may have to be considered, using doses of about 300 milligrams a day. With this the risk of damage to the fœtus described by Harris and Ross (1956) does not usually enter into consideration as these anæmias are found in the later part of pregnancy after the child is fully formed. In some cases splenectomy or even Cæsarean section may become necessary as a last resort.

THE ANÆMIA OF TOXIC AND INFECTIVE STATES

Under this heading come the anæmias found in nephritis, chronic infections, and the rheumatic group of diseases, particularly rheumatoid arthritis. The blood picture varies from case to case and is often microcytic normochromic, but sometimes even microcytic hypochromic. In the latter case the fault may not be a simple iron-deficiency and the bone marrow may contain ample quantities of stored iron. Each case has to be considered on its own, but the severer of these may well call for transfusion before delivery.

Aplastic anæmia in pregnancy has been described.

THE ANÆMIA OF OTHER HÆMATOLOGICAL DISORDERS

The anæmia accompanying *leukæmia* is a rare complication of pregnancy. Treatment is most unsatisfactory, for the cytotoxic and anti-folic acid drugs and x-ray treatment are contraindicated. Cortisone might be tried and blood transfusions given when necessary. The leukæmia does not affect the fœtus and the only consolation in this horrible disorder is that the child may be born healthy (Beven, 1951; Allan, 1954; and Harris, 1955).

The anæmia associated with *thrombocytopenic purpura* is but a small part of this dangerous disorder and is proportional to the extent of the hæmorrhages. Some of the cases recorded during pregnancy have settled down, but repeated blood transfusions may be necessary in severe cases (Hammond, 1952), and even an emergency splenectomy may have to be considered.

SUMMARY

As anæmia results in considerable maternal morbidity the causes should be sought and corrected.

An anæmia found during pregnancy can be either a pre-existing anæmia possibly aggravated by pregnancy, or an intrinsic anæmia induced by the physiological demands of pregnancy outweighing the uptake of essential materials and necessitating diversion of these from the woman's own blood-forming tissues.

The anæmia of pregnancy is mainly an iron-deficiency anæmia. The 'physiological anæmia', due to simple hæmodilution, is a doubtful entity. Severe anæmia endangers the woman's life in labour, lesser degrees add to her household difficulties during pregnancy and if left untreated predispose to severe chronic anæmia. It is therefore important to see that women are well nourished and properly cared for during their pregnancies.

As clinical assessment of all but the severe degrees of anæmia is difficult or impossible, screening by a hæmoglobin estimation at the 32nd week should be included in the care of all pregnant women. Any anæmia of clinical importance is likely to be present by then and there is still time to treat those women who are found to have a hæmoglobin level below 12 grammes per 100 millilitres (80 per cent. Haldane). The giving of iron and other tablets indiscriminately at clinics is a poor alternative.

In a small number of women the anæmia does not respond to oral iron treatment. The majority of these have some absorptive defect and respond to parenteral iron. A minor group are iron refractory and some of these can be attributed to toxic complications such as urinary infections.

In a minor group, 1 to 2 per cent. of all cases, the anæmia is not due to iron deficiency. The most important of these anæmias is the megaloblastic anæmia of pregnancy. If missed this can have serious consequences for the mother. The diagnosis may be suspected from the peripheral blood, but it should be established by a bone marrow examination before folic acid treatment is started.

Very rarely the anæmia is found to be of a hæmolytic type and this may recur in subsequent pregnancies.

Almost equally rarely pregnancy occurs during the course of other anæmias, pernicious anæmia, chronic hæmolytic anæmia, and the anæmias of other hæmatological conditions including leukæmia. The problem is then the underlying disorder.

I wish to thank Mr. William Rivers, of the department of bacteriology, King's College Hospital Medical School, for the photomicrographs.

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ANÆMIA IN INFANCY AND CHILDHOOD

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Few disorders of the blood are not accompanied by anæmia of one form or another and the types of secondary anæmia which infants and children are prone to are many. Knowledge of blood diseases, blood formation and blood destruction is accumulating at a great rate and with our increased understanding of many disease processes our ability to deal with the resultant secondary anæmias is growing. Advances in diagnosis as well as in treatment are made with such regularity, particularly because of the introduction of new techniques such as tissue culture and radioisotope tagging, that it is increasingly difficult for workers, even in the same field of a narrow specialty, to keep pace with each other's advances. It is my intention to discuss some of the newer items of knowledge concerned with anæmia in childhood which to me seem important, it being fully realized that the anæmia discussed is often entirely secondary to some other misfeasance of the blood-forming organs.

ERYTHROBLASTOSIS FŒTALIS

In the majority of cases erythroblastosis fœtalis, or hæmolytic disease of the newborn, is due to incompatibility of the Rhesus blood factors of mother and child. In a small proportion of cases other factors are involved and the number of these factors is growing at an alarming rate. Kell, Lutheran and Lewis of a few years ago have been added to within the last year and most of these factors have already been shown to give rise to hæmolytic anæmia. The rarity with which they give rise to clinical trouble, however, is so great that it is not necessary to remember them. The presence of antibody to them, though not its specificity, will be inferred by the finding of a positive direct Coombs test with the affected baby's red cells; the specificity of the antibody and the selection of compatible blood thereafter are matters for a few reference laboratories. What appears to be more important is that it is now generally conceded that incompatibility within the ABO blood groups may also give rise to hæmolytic disease of the newborn and, on occasion, kernicterus. With nearly half the population group O and half group A or B the number of marriages in which a group O mother will conceive a group A or group B fœtus is obvious; so common will this be that it appeared most improbable that the maternal anti-A or anti-B agglutinin could so seriously affect the fœtus; yet that this can happen on rare occasions is now well authenticated.

How Rhesus antibodies may deleteriously affect the fœtus has recently been indicated by Chown (1955), who showed that the red cells of a fœtus

aged 6 weeks were already coated with Rhesus antibody derived from the maternal circulation, the same antibody also being present in the fœtal serum.

Exchange transfusion, following the pioneer work of Diamond (1947) and the careful trials of Mollison and Walker (1952) and their collaborators, has been shown to be the treatment of choice in erythroblastosis fœtalis, the level of hæmoglobin and serum bilirubin in the cord blood being used as an indication of whether exchange transfusion will be necessary. Sometimes, as indicated by a rising serum bilirubin, a second exchange transfusion may have to be performed; this procedure has been shown to be not only lifesaving but to reduce the incidence of the much-to-be-feared kernicterus. Now that treatment of the fœtus is possible it is the more important to ensure that the maternal Rhesus state and presence or absence of antibodies shall be determined before birth.

KERNICTERUS

Until recently it was thought that kernicterus was always caused by blood-group incompatibility but, following the work of Aidin, Corner and Tovey (1950) and Govan and Scott (1953), it is now realized that, in the absence of any maternal antibodies, premature babies may develop classical kernicterus. It is not finally resolved whether this is due to fœtal anoxia or immaturity of the brain, or a combination of both these and other factors; but that prematurity can be associated with kernicterus should be borne in mind in considering early induction of labour to enable the fœtus to escape some of the action of maternal blood-group antibodies in the last stages of pregnancy.

CONGENITAL NON-SPHEROCYTIC HÆMOLYTIC ANÆMIA

Acholuric jaundice is a well-defined and readily diagnosed condition in which splenectomy can confidently be expected to cut short the patient's symptoms. A considerable number of cases of anæmia are seen, however, in which the spherocytosis so characteristic of acholuric jaundice is not present and in which there is no increased osmotic fragility of the red cells. Such patients may show other abnormalities of red cell shape such as anisocytosis and some degree of elliptocytosis. They tend to occur in families and behave in a similar fashion to cases of true hereditary spherocytosis in that they are often anæmic, occasionally slightly jaundiced, there may be splenomegaly and there are definite episodes corresponding to minor hæmolytic crises in which the condition is exacerbated; their response to splenectomy is less noteworthy than in the spherocytic type, although removal of the spleen may sometimes cut short a history of chronic ill health in childhood.

ACUTE ERYTHROBLASTOPENIA

In this condition, which has recently been recognized by Gasser (1951), anæmia is brought on because of a sudden disappearance of the red-cell precursors in the marrow. The condition tends to recur and is thought to

be due to some form of allergy. The bone marrow recovers spontaneously in the course of some days or weeks and the anæmia corrects itself. Other allergic manifestations may also be present to give a clue to the cause of the anæmia.

IDIOPATHIC THROMBOCYTOPENIC PURPURA

Our understanding of some cases of this condition has been advanced by the demonstration by Stefanini and Dameshek (1953) that an antibody to platelets may develop in a way analogous to the antibody in acquired Coombs-positive hæmolytic anæmia. This is probably the reason why some cases respond so favourably to cortisone which will damp down the production of antibodies, even to the extent of producing a complete remission. The anæmia occasioned by overt bleeding due to lack of platelets is less to be feared than the internal bleeding, particularly intracranial, which may occur in the condition.

COAGULATION DEFECTS

The classification of various types of coagulation defect now recognized—and their number is being increased annually—is a laboratory exercise calling for much time and ingenuity. There are some 9 or 10 factors known to be involved when blood clots to stop hæmorrhage, and a deficiency of any one or more of these may give rise to intractable bleeding and profound anæmia. The correction of the anæmia nearly always necessitates blood transfusion, whilst to stop bleeding it may be sufficient in a case of true hæmophilia to give an intravenous injection of anti-hæmophilic globulin. Much knowledge of the clotting factors is not necessary but, whilst true *hæmophilia* is still restricted to males the other factors, when deficient in females, may give rise to a condition indistinguishable from hæmophilia but occurring in a girl. Such a condition calls for a full laboratory investigation and should not be called true hæmophilia.

One old, but recently delimited, condition causing abnormal bleeding is *von Willebrand's disease*, in which a prolonged bleeding time occurs although all the factors necessary for clotting are normal. The cause of this bleeding, which may lead to profound anæmia, seems to be a periodic capillary weakness. The importance of von Willebrand's disease is that it is familial and occurs equally in girls and boys. When these children are in a bleeding phase they should be carefully protected from injury. When the bleeding time is normal, however, major surgery may be carried out with perfect safety.

IRON-DEFICIENCY ANÆMIA

Although many factors have been cited as being concerned with erythropoiesis, the only really essential factors appear to be iron for hæmoglobin and cyanocobalamin and folic acid for the synthesis of nucleic acid. All the other factors, such as copper and cobalt, are sufficiently freely available in the ordinary diet as to be most unlikely to give rise to symptoms in the human. True, an anæmia of pigs appears to be related to copper deficiency,

but Cartwright (1955) points out that it is almost impossible to compose a diet containing insufficient copper. Zinc and molybdenum are other trace metals which have been implicated in iron metabolism, but their role in man is not yet determined. Cobalt is present in cyanocobalamin, but otherwise what it might do in the absorption of iron remains vague.

Apart from direct loss of iron due to hæmorrhage, a deficiency of iron in infancy and childhood may be caused by insufficient iron reserves at birth, insufficient dietary intake or interference with the absorption of iron from the duodenum. There is also the iron-deficiency anæmia associated with chronic infection, the mechanism of which is remarkably little understood. As something like one-tenth of the dietary iron is absorbed, if the normal adult diet contains 12 to 15 mg. of iron a day, not more than 1.5 mg. a day will be retained. Moore (1955) concludes that the daily loss of iron in sweat, urine and desquamated skin cells is about 1 mg. a day. During pregnancy the mother must provide 300 to 500 mg. of iron, or 1 to 2 mg. a day, for her baby. These figures suggest that iron-deficiency anæmia may easily arise in the mother during pregnancy and lead to a diminution in the store of iron with which the new-born baby sees himself through the early stages of life.

Inadequate dietary iron is classically seen in prolonged breast feeding when the iron content of the mother's milk is insufficient to supply the needs of the growing baby. The anæmia of prematurity, again, is closely related to inadequate stores of hæmatinics in the infant.

The preparations of iron for correction of iron deficiencies most favoured at present are ferrous gluconate and ferrous succinate and these have tended to supersede the older iron compounds, such as ferrous sulphate, because they are better tolerated and have higher utilization factors (Haler, 1952). Ferrous gluconate is given in a dosage of 200 mg. three times a day at birth, rising to 500 mg. at one year; this dose is somewhat higher than that used for ferrous sulphate or iron and ammonium citrate.

For those patients who do not tolerate oral iron preparations well, or who fail to utilize ingested iron, an *intravenous* preparation has been elaborated: saccharated iron oxide. Its use has special drawbacks in children because it must be injected intravenously and *without extravasation* and because of its toxicity. It is dispensed as 100 mg. in 5 ml., and a first injection should not exceed 1 ml. of this.

Intramuscular iron preparations are now available and are as effective as intravenous iron although the response is slightly slower (Cope, Gillhespy and Richardson, 1956). Under the name of 'imferon' intramuscular iron is dispensed as 50 mg. of iron in 1 ml. There are various formulæ to determine the total amount of iron necessary to correct a given degree of anæmia, allowing for an excess of iron to replenish the body reserves. To babies under 8 lb. (3.5 kg.) not more than 0.5 ml. should be given at one injection; from 8 to 20 lb. (3.5 to 9 kg.) not more than 1 ml. and in bigger children not more than 2 ml.

The response of iron-deficiency anæmia to intramuscular iron is certainly quicker than when oral iron is given, but the modern oral preparations are to be preferred except when clinical trial indicates some other form of administration (Moore, 1955). One of Moore's most important findings was that ascorbic acid usually increases the assimilation of iron from food and there is thus a cogent reason for the dispensing of iron and ascorbic acid together, this being probably the only degree of polypharmacy which should be permitted in the treatment of iron-deficiency anæmia.

HÆMORRHAGIC DISEASE OF THE NEWBORN

Because vitamin K has been shown to be useful in the prevention, as well as the treatment, of this condition, it has been used widely as a prophylactic in the newborn, generally in the form of 'synkavit'. Because of its apparent harmlessness there has been a tendency in the past decade to increase the dosage more and more 'to be on the safe side'. Gasser (1953) was the first to wonder whether vitamin K was the cause of severe hæmolytic anæmia in premature babies, and Laurance (1955), Allison (1955) and Meyer and Angus (1956) showed that an increase in the incidence of kernicterus coincided with an advance in the routine prophylactic dosage of vitamin K from 2 mg. to 10 mg. or more. Now that the toxic potentialities of 'synkavit' have been amply demonstrated a dose of 1 to 2 mg. has been reverted to and should not be exceeded.

PLATELET TRANSFUSIONS

Anæmia due to bleeding because of a deficiency of platelets occurs not only in idiopathic thrombocytopenic purpura but in many examples of secondary thrombocytopenia, such as leukæmia, reticulosis and acute infectious thrombocytopenia (Stransky and Lim, 1956). A recent advance, due to the development of plastic materials, has been the ability to transfuse platelet suspensions to these patients (Stefanini and Dameshek, 1953). The technique is likely to be particularly used to cover urgent surgical procedures such as splenectomy or to stop dangerous hæmorrhage. The life of a platelet appears to be seven to eight days, and in the case of congenital hypoplastic thrombocytopenia studied by Doyne Bell, Mold, Oliver and Shaw (1956), platelet transfusions were able to establish a normal bleeding time for periods up to twelve days. In their case the development of a platelet antibody following repeated transfusions terminated the usefulness of the procedure.

SPLENECTOMY

This operation, after a period in the doldrums, is being undertaken more readily in an increasing number of conditions. The role of the spleen in inhibition of the marrow and in blood destruction is still imperfectly understood and the success of splenectomy for the treatment of some hæmatological conditions is generally based upon empirical observations. Splenectomy, which, because of our tendency to regard it as major and dangerous

surgery, is often the ultimate therapeutic procedure, is often the only treatment in acquired hæmolytic anæmia and in splenic anæmia. It should be performed in hereditary spherocytosis when this condition interferes with the leading of a normal life. It may ameliorate the condition of non-spherocytic hæmolytic anæmia and has been shown to improve the health of patients with congenital elliptocytosis. Splenectomy should be carried out in cases of idiopathic thrombocytopenic purpura which have had recrudescences for more than a year, and the operation may assist the survival of patients with leukæmia, particularly when this is associated with hæmolytic antibodies.

CORTISONE

Although cortisone appears to have no curative properties, it has found a place in the treatment of the anæmia in various conditions. Children with leukæmia responding favourably increase their hæmoglobin and may correct entirely the anæmia which is the most common presenting symptom of leukæmia. It may abate the hæmolytic process in acquired hæmolytic anæmia, and may cut short an attack of bleeding in thrombocytopenic purpura, possibly through its action in depressing platelet antibody formation; it is thus often used as a precursor to splenectomy in these conditions. In the rare cases of erythrogenesis imperfecta cortisone may enable the blood transfusions obligatory for the survival of the patients with this disease to be abandoned (Kåss and Sundal, 1953; Fisher and Allen, 1953; Calvert and Robson, 1956). It is to be noted that when the hæmoglobin rises under treatment with cortisone the red cells always increase in size and a high colour index is produced.

In one child with erythrogenesis imperfecta treated with cortisone at Great Ormond Street, progress was recorded by twice-weekly hæmoglobin estimations only. The hæmoglobin content of the blood rose from 45 per cent. to 75 per cent. (or from 6.66 g. to 11.00 g. per 100 ml.) and the child was much improved and needed no blood transfusion during a period of six months. Yet, at the end of this time the red cell count was practically the same as at the beginning of treatment—2,700,000 per c.mm.—and the apparent correction of the anæmia had been made by increasing the size and hæmoglobin content of the red cells.

A similar population of large red cells is always found in the peripheral blood of cases of leukæmia under treatment with cortisone and, to a lesser degree, in treated cases of acquired hæmolytic anæmia.

LEAD POISONING

Babies and young children are particularly prone to lead poisoning because of their habit of sucking things. Whilst the discontinuance of the use of lead in children's playthings and the development of non-lead-containing paints has undoubtedly diminished the number of children seen with anæmia due to lead poisoning, the number showing pica does not diminish and lead poisoning is still encountered. Until recently there has been none but expectant treatment for the anæmia and other stigmata of lead poisoning, but the introduction of chelating agents into therapeutics has given us a new

weapon with which to combat lead poisoning. The one used is the calcium disodium salt of ethylenediamine tetra-acetic acid marketed under the name of 'versenate'. The affinity of lead for 'versenate' is greater than that of calcium, and lead will displace calcium from 'versenate' in the body to produce a lead disodium chelate which is very stable and soluble and readily excreted in the urine. 'Versenate' was first used by Bessman, Ried and Rubin (1952) for the successful treatment of lead poisoning. Unfortunately, it appeared that the drug had to be given intermittently by the intravenous route over a period of several days: an obvious drawback in toddlers which has led to other methods of administration being tried.

The drug has been given by mouth (Bradley and Powell, 1954), but it is much less effective and is considerably toxic by this route. Now it has been shown by O'Donohoe (1956) that subcutaneous administration of 'versenate' can be successfully employed. The dose used was 25 ml. of a 1 per cent. solution of 'versenate' in normal saline every six hours for five days subcutaneously; hyaluronidase, 1,500 units, was included with each dose, which took about thirty minutes to give. The total dose of 'versenate' was 5 g., no local complications occurred, the urinary lead concentration increased markedly, the hæmoglobin rose slowly, punctate basophilia of the red cells disappeared and the lead lines present on x-ray examination of the bones diminished gradually. This chelating agent therefore clearly has a place in the treatment of lead poisoning. Whether more concentrated 'versenate' could be given in smaller quantities of saline and at longer intervals of time remains for investigation.

DISCUSSION

It will be readily appreciated from the varied nature of the subjects discussed here, which do not include any of the most recent work with radioisotopes, that the subject of anæmia in infancy and childhood—causative, preventive and therapeutic—is advancing on a wide front. At first sight much of the work may appear to be highly scientific and of little practical application and, indeed, of much of the recent work this accusation is true. Yet, when a subject is developing so rapidly, today's laboratory wonder is tomorrow's routine clinical practice. Of the random subjects discussed here the following, however apparently academic, are of immediate everyday interest and application:—

The importance of ensuring that the Rhesus state of all pregnant women is known so that where they are Rhesus-negative routine checks for antibodies may be performed and the treatment of hæmolytic disease of the newborn instituted in timely fashion.

The appreciation of the phasic nature of von Willebrand's disease and the knowledge that during the intervals of remission a full and, if necessary, vigorous life may be led (one of MacFarlane and Simpkiss' (1954) patients became a champion boxer of the Royal Navy).

A broader knowledge of iron metabolism has meant that the improved

preparations and new methods of administration of iron can be readily adopted in routine practice.

The fact that the dosage of 'synkavit' could not be readily increased with impunity in the prevention of hæmorrhagic disease of the newborn has immediately borne fruit in the reduction of cases of kernicterus.

The development of anti-metabolic drugs in the treatment of leukæmia has enabled anæmic children to be discharged home where further treatment may be undertaken with maintenance cortisone, and a knowledge of cortisone and its effects on both anæmia and general bodily function has become necessary.

Whilst the treatment of lead poisoning is unlikely at present to be undertaken except in hospital, the development of knowledge of how to use 'versenate' in this condition means that lead poisoning may well become in the foreseeable future a disease to be treated by the family doctor.

Certain subjects, such as the anæmia of sepsis and the anæmia accompanying chronic nephritis, have hitherto withstood many attempts at elucidation, but it is to be hoped, and indeed expected, that as the newer methods for the study of blood formation and destruction by means of radioisotopes are elaborated, we shall come to understand the mechanisms whereby these and similar anæmias are brought about; with a knowledge of their causation we may be able to prevent them.

Much of this anticipated advance in knowledge must inevitably be concerned with iron metabolism and the formation of hæmoglobin and when these have been better worked out it seems likely that much of the anæmia at present seen in hospital practice will be prevented in the home.

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HÆMOPHILIA AND RELATED HÆMORRHAGIC DISORDERS

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DURING the past decade investigation of hæmorrhagic diseases has led to a greater understanding of the fundamental processes of blood coagulation and to a more rational approach in the treatment of its disorders. The confusion engendered through the use of the varying nomenclature by authorities in this field is regrettable though understandable because of the gross and often difficult methods used in testing for trace proteins and enzymes in this process. Since the larger number of these disorders are congenital and appear early in life, patients with classic hæmophilia and related hæmorrhagic diseases are usually first seen by the pædiatrician. It is hoped that this review of 100 patients studied at the Children's Hospital during the past eighteen months may help to clarify some of the problems presented by a 'bleeder' and result in further interest in, and improved care of, these children.

BASIS OF PRESENT REPORT

The largest number of this group (80 patients) have been proved to have classic hæmophilia, in which a deficiency of antihæmophilic factor (AHF) is postulated. Fourteen others exhibit a clinically similar but biologically distinct abnormality termed plasma thromboplastin component (PTC) deficiency (Aggeler *et al.*, 1952) and named 'Christmas disease' after a child, Stephen Christmas, studied by Biggs *et al.* (1952) in England. Three others have combined abnormalities of the blood vessels and antihæmophilic factor, which have been termed 'pseudohæmophilia' or von Willebrand's disease (von Willebrand, 1926, 1931; MacFarlane, 1941; Alexander and Goldstein, 1953). Another three patients with abnormal bleeding of a mild degree have a deficiency of plasma thromboplastin antecedent (PTA) as described by Rosenthal and his group (1953,1955). All of these children have had one or more manifestations of abnormal bleeding with easy bruisability, prolonged hæmorrhage from lacerations, nose bleeds, operative procedures or bleeding into joints, muscles, and internal organs from minimal trauma. The severity of these manifestations is greatest in those with classic hæmophilia, and is progressively milder in each of the other conditions. The age distribution ranged from birth to 16 years. The period

of study, for statistical purposes, covered the past five years (1950-55).

THE THREE PHASES OF BLOOD COAGULATION

At present the coagulation of blood is thought to be divided into three phases, consecutive and, according to some investigators, interdependent.

Phase I.—*The generation of thromboplastin* from platelets, antihæmophilic factor (AHF), Christmas factor (plasma thromboplastin component; PTC), plasma thromboplastin antecedent (PTA), possibly additional factors (Spaet *et al.*, 1954) and calcium—all except for platelets present in normal plasma.

Phase II.—*The conversion of prothrombin into thrombin* by the action of thromboplastin.

Phase III.—*The conversion of fibrinogen into the fibrin clot* by the action of thrombin.

'Prothrombin accessory factors', i.e. proconvertin and proaccelerin (Owren, 1953) are necessary integral substances which act in phase II and possibly

	AHF	PTC	PTA
Normal plasma	Present	Present	Present
Normal serum	Absent	Present	Present
Stable on storage at 4° C.	No	Yes	Yes
Precipitated by barium sulphate	No	Yes	Partially
Site of production	? reticulo-endothelial	Liver	?
Deficiencies	Classic hæmophilia 'Hæmophiliod' states	Christmas disease Liver disease ? Vitamin K deficiency Hæmorrhagic disease of the newborn	PTA deficiency
Clinical effect of administered plasma	4 to 6 hours	2 to 3 days	Less than 7 days
Probable amount required for normal clotting time	15%	5%	? 15%

TABLE I.—Differences between AHF, Christmas factor (PTC), and PTA.

in phase I. Exactly what reactions initiate phase I is widely discussed at present (Conley *et al.*, 1949; Rappaport *et al.*, 1955). It appears likely that electrostatic changes on contact with a surface other than that of the intact blood vessel alter protein structure and function to initiate clotting (Sawyer and Pate, 1953). Evidence has been advanced that the enzymatic activity of some of these substances is increased during coagulation whilst others disappear (Alexander *et al.*, 1949; Owren, 1952). It is probable that some substances, which occur normally as well as in pathological states, tend to inhibit these reactions and to remove fibrin once it has formed (Alexander, 1955).

The differences between AHF, Christmas factor (PTC) and PTA, are summarized in table I, whilst table II summarizes the screening tests to be performed in a patient suspected of having hæmophilia.

GENETIC ASPECTS

Of the 69 families with classic hæmophilia, a sex-linked recessive pattern of transmission was present in 65 per cent., and among the 12 families

Screening test	If abnormal, proceed in sequence to
1. Clotting time and visual gross clot retraction.	Cross-protection test by prothrombin consumption or recalcification times and thromboplastin generation test.
2. Bleeding time.	Microscopic examination of capillaries, quantitative clot retraction and thromboplastin generation test.
3. Platelet count and examination of blood smear.	
4. Quick 'prothrombin' time.	Quantitative prothrombin, proconvertin, pro-accelerin and fibrinogen.
5. Prothombin consumption.	Cross-protection test by prothrombin consumption or recalcification times, quantitative clot retraction and thromboplastin generation test.

TABLE II.—Screening tests performed on a patient suspected of having classic hæmophilia or related disorders.

All the tests in the *left column* are performed on a suspected 'bleeder' as screening procedures. If all are normal, the patient is considered normal provided that *his history is not strongly suggestive of a hæmorrhagic tendency*. 1 and 5 are abnormal in classic hæmophilia and Christmas disease, 2 in von Willebrand's disease. All may be normal in PTA. In either case, the procedures in the *right column* are performed as more refined tests to rule out minor abnormalities. (See text for interpretation).

with Christmas disease, in 60 per cent. The abnormality in each is transmitted through female 'carriers' and is manifested in affected males.

These figures are in agreement with other published series (Biggs and MacFarlane, 1953) and indicate that in over a third of all such children, the defect has occurred in the presently studied generation without a positive family history. Some investigators, e.g. Andreassen, 1943, have suggested, but others have refuted (Mersky and Macfarlane, 1951), that mild degrees of AHF deficiency may occur in female siblings and that by proper techniques those females who are 'carriers' may be identified. Although several of our patients' mothers have suggestive histories of abnormal bleeding and have shown slight but reproducible defects in the generation of thromboplastin, we do not feel that our evidence is statistically valid to predict this defect in female carriers. Severe classic hæmophilia has been reported in females in whose families both parents apparently possess the defective gene (Israëls *et al.*, 1951). We have not encountered such a case. The severity of the coagulation defect remains the same throughout the patient's life and usually is manifested to similar degree in affected siblings. Mild forms of AHF and PTC deficiency have been studied in which an allelic form of the defective gene is postulated (Brinkhous *et al.*, 1954). These patients usually do not manifest serious bleeding tendencies except under stress and may have an almost normal clotting time. Eleven of our children with classic hæmophilia and six with Christmas disease fall within these groups. The amount of AHF may vary between 3 to 10 per cent. of normal adult levels. We have not measured the degree of Christmas factor deficiency.

PTA deficiency, on the other hand, appears to be transmitted by a Mendelian dominant gene with incomplete penetrance (Rosenthal *et al.*, 1953). In one of our two families with this disease, the mother and one of three children have histories of abnormal bleeding and characteristic thromboplastin generation tests. We have little evidence for the genetic

transmission of von Willebrand's disease ('pseudohæmophilia'), although in one family the father and the only son are affected. A Mendelian dominant type of inheritance has been postulated (MacFarlane, 1941).

CLASSIC HÆMOPHILIA AND CHRISTMAS DISEASE

The clinical manifestations of classic hæmophilia and Christmas disease are almost identical. It was only upon administering blood from one patient to

Type of abnormal bleeding	Incidence in 94 patients (per cent.)	Type of abnormal bleeding	Incidence in 94 patients (per cent.)
Dental extractions (27 patients)	100	With development or loss or primary dentition	21
Appendicectomy, tracheotomy and other operative procedures	100	Severe hæmorrhage into tissues of neck	18
'Easy bruising'	90	Following infection	15
Hæmarthroses	90	Following dental extraction	3
Intramuscular	82	Nervous system	16
Epistaxes—repeated	67	Peripheral nerve palsy	9
Mucous membranes of mouth, tongue, and frenulum	60	arm: ulnar nerve	3
Neonatal period (29 patients)	35	leg: femoral, lateral femoral cutaneous nerves	6
Following circumcision	32	Central nervous system	7
Intracranial	2	Gastro-intestinal	10
Umbilical	1	Mortality	
Genito-urinary	26	Severe intracranial hæmorrhage—2 patients	
Intra-abdominal and retroperitoneal	24	During tracheotomy for severe hæmorrhage into neck—1 patient	
With development or loss of permanent dentition	24		

TABLE III.—Incidence of clinical manifestations in 94 patients with classic hæmophilia and Christmas disease.

another (both of whom were considered to have classic hæmophilia) and finding mutual correction of their defects, that the difference between these two diseases was first recognized (Pavlovsky, 1947; Schulman and Smith, 1952). The following findings (table III) include the clinical manifestations of these conditions in 80 patients with classic hæmophilia (also termed hæmophilia A) and 14 with Christmas disease (also termed hæmophilia B).

BLEEDING IN INFANCY

Since these diseases are congenital, it is not unusual that 35 per cent. of the infants manifested abnormal bleeding tendencies within the first ten days of life. Antihæmophilic factor is absent from the cord blood of a child with this defect. One infant bled from the umbilicus, two had intracranial hæmorrhage and 26 bled following circumcision. The latter is often severe enough to require plasma or whole blood administration (four cases with mild classic hæmophilia and two with congenital PTC deficiency had no abnormal bleeding with, or following, circumcision). These infants also

have physiologically low Christmas factor, prothrombin and proconvertin levels and poor formation of thromboplastin. Their protected environment undoubtedly lessens the high risk of hæmorrhage.

During the first three years of life 60 per cent. of these patients have had prolonged bleeding from small lacerations of the lips or mucous membranes of the mouth. Such lesions are apt to bleed for several days. Constant washing with saliva prevents adequate hæmostasis and the clots are soft and fragile. We admit these infants to hospital, and administer sedatives and plasma infusions for three days or until adequate clot formation has occurred. An attempt is made to keep the bleeding area dry and free of saliva but in small children, local hæmostatic measures are often difficult to apply. Ice applied to a bleeding area in the mouth has often delayed adequate clot formation and prolonged the bleeding. Two children first developed subcutaneous hæmatomas following immunization injections. We recommend that each child receive routine immunizations but that these be given carefully; with local application of ice and pressure dressing no untoward reactions have occurred.

DENTAL CARE AND EXTRACTIONS

Appearance and loss of decidual teeth infrequently caused prolonged bleeding and could be handled by local application of hæmostatic agents. Early and adequate dental prophylaxis is important, for extraction of teeth with resultant tearing of tissue has caused severe and dangerous bleeding. We urge that all patients have regular dental examinations after their second year of life. Occasionally the gums bleed from vigorous brushing; this usually stops spontaneously.

Twenty-two children have had extraction of teeth for caries. Since the institution of planned therapy, complications from this procedure have been unusual. Should extraction be necessary, the patient is admitted to the hospital and given plasma infusions immediately before, during and for two to four days afterwards. Gentle surgical care is exercised and the tooth socket is packed with 'gelfoam' or 'oxycel' soaked in a concentrated solution of 'topical thrombin (bovine)'. At times gentle manual pressure must be maintained over the socket for several hours. Prostheses and other mechanical devices designed to maintain pressure over the area (Birch, 1937; Davidson *et al.*, 1949) have not been practical in small children. The patient is given nothing by mouth. Should bleeding occur, it usually happens during the second or third day after extraction. The inadequate soft clots are then completely removed, a new freshly prepared pack is introduced and plasma is administered for two more days. An attempt may be made to keep the area dry with cotton packs and suction. On the third day, a fluid diet is started. The potential danger from bleeding is not passed until after the 6th day.

Suturing of a bleeding area or the margins of the socket *is* distinctly *contraindicated.*

GASTRO-INTESTINAL AND GENITOURINARY BLEEDING

Gastro-intestinal hæmorrhage is unusual (10 per cent.) and mild, even when associated with diarrhœa, in infancy. Rarely it may be difficult to control. Bed rest, antispasmodics, and continuous whole blood and plasma infusions tided one child over a three-week period of massive melæna. A suspected peptic ulcer healed with medical treatment. Hæmaturia (26 per cent.) may follow trauma to the renal area and occurs mainly in those with severe clotting defects. Despite plasma infusions such hæmorrhage usually lasted ten days to two weeks. Recently, we have been able to reduce this period by combining oral cortisone with plasma infusions.

BLEEDING INTO CRANIUM OR NECK

Hæmorrhage into or around the brain following trauma (7 per cent.) and into the soft tissues of the neck (18 per cent.) secondary to croup, severe pharyngeal infections and massive bleeding into tissues following dental extraction (3 per cent.) are major complications. Absolute bed rest, constant plasma infusions and, at times, steroid therapy, combined with fine surgical judgment, must be used in every such situation. Even so serious a problem as that of a 4-month-old infant with a fracture of the skull and massive repeated subdural and epidural hæmatomas was recently treated successfully with plasma infusions and surgical intervention. Of the three deaths in this series, two followed intracortical brain hæmorrhage secondary to severe trauma (Chalgren, 1953) and one resulted from tracheal compression, the child having arrived at the hospital *in extremis*. In the case of bleeding into the neck, care must be taken that an adequate airway is always present. All except three cases with such complications were associated with inadequately treated pyogenic pharyngeal infections and occurred on the 2nd to 4th day of illness. Our patients are strongly urged to seek medical attention at the earliest sign of any infection, since their tendency to bleed is increased during this time.

SURGICAL PROCEDURES

Two children have survived tracheotomy, although we are reluctant to perform this procedure and have successfully used medical measures alone in the last eight instances of pharyngeal bleeding. Constant nursing care and close observation are necessary. We have not employed intubation (MacDonald *et al.*, 1953) for fear of increasing local hæmorrhage. Three others have undergone successful appendicectomies while receiving continuous fresh-frozen plasma infusions. Two of these developed minor postoperative bleeding into the wound.

In cases in which surgical treatment is necessary, we believe that these children should be treated as one would a patient without hæmophilia, provided the hæmophiliac is receiving adequate constant replacement therapy with plasma. No deaths have occurred as a result of surgery. Our experiences do not agree with the previously reported major surgical mor-

tality of 20 to 35 per cent. in hæmophiliacs (Davidson *et al.*, 1949; MacDonald *et al.*, 1953).

BLEEDING INTO JOINTS

The most common site of serious repeated hæmorrhage in these patients is into the large joint cavities of their extremities: 85 per cent. have experienced such episodes first occurring between 18 months and 3 years of age. Most often such bleeding follows a twisting injury which is often unnoticed by the patient. All our patients with classic hæmophilia, and 10 of the 14 with Christmas disease, have had hæmarthroses after 6 years of age. Of the group with classic hæmophilia, 15 per cent. are less than 3 years of age and of these, half have not had joint hæmorrhages.

At the first symptom of pain, we urge that the patient rest the extremity and curtail weight bearing. Should the signs of hæmorrhage continue, the child is seen together by the medical and orthopædic services in this hospital and his care remains their mutual responsibility. In all cases, initial coagulation studies are performed to substantiate the diagnosis of a hæmorrhagic disease and its response to plasma. With slight bleeding, the joint is placed at rest by immobilizing the extremity in a bivalved plaster case. If a large hæmorrhage is present, the child is admitted to the orthopædic ward where blood may be aspirated from the joint under local or general anæsthesia. Our experience with agents to increase the absorption of blood (hyaluronidase) has not been impressively different from that employing aspiration alone. Plasma infusions are begun at the time of aspiration and continued at six-hour intervals until signs of active bleeding have diminished. These signs are objective—from the size of the joint—and subjective—from the disappearance of pain without the joint cavity. A pressure dressing or a plaster cast, which is soon bivalved, is applied to provide an initial phase of complete immobilization and rest. Ice packs, sedation and, rarely, narcotics may be necessary to relieve pain. Cold packs may also diminish further local hæmorrhage through vasoconstriction.

Several days after bleeding has stopped, gentle passive physiotherapy is begun to prevent the development of joint contractures. If hæmorrhage into the joint cavity and surrounding tissues causes sufficient muscle spasm to produce flexion deformity, gentle traction (up to 4 to 6 lb. [1.8 to 2.7 kg.]) is applied to restore motion and alignment. Weight bearing should be avoided for several weeks or months through the use of orthopædic aids. It is felt that the first hæmorrhage causes structural damage which may heal completely with restoration of normal joint function. Repeated hæmarthroses into the same area (which occur before the previous one has had time to heal completely) lead to destruction of joint cartilage and serious ankylosis. Such periods of forced immobility are difficult for the young child to understand and create trying times for the parents. Unfortunately, despite these measures about 40 per cent. of our patients who have had repeated hæmarthroses have developed moderate to severe functional impairment.

BLEEDING INTO MUSCLES

Small hæmorrhages into muscles are usually not serious and are treated with plasma infusions and pressure dressings. Hæmorrhage into a deep fascial compartment containing blood vessels and nerves, on the other hand, causes intense pain and protective flexion may result in ischæmia of the distal parts and irreparable damage to the nerves. This is akin to Volkmann's ischæmic paralysis. The swelling is deep within the tissues and difficult to palpate. It should be recognized early.

With large hæmorrhages it is advisable to attempt to evacuate blood by aspiration if localized collections are present. Whether or not surgical incision and drainage should be employed depends upon the individual patient's condition. Early treatment, consisting of plasma infusions, bed rest, elevation and immobilization of the extremity in plaster casts, has prevented most such complications during recent years. Physiotherapy is started early and function may return gradually over a period of months. Two patients had developed ischæmic paralysis of the arms before being seen here. Two others have suffered femoral nerve palsies from hæmorrhage beneath the inguinal ligament.

NOSE BLEEDS

Nose bleeds, though frequent, have seldom been serious. The bleeding point is visualized and small 'gelfoam' packs soaked in 'topical thrombin' solutions are applied with gentle pressure. The cautery should not be used since destruction of tissue by this means usually leads to further bleeding.

LACERATIONS AND SUBCUTANEOUS HÆMATOMAS

Lacerations are not sutured unless the patient is receiving replacement therapy, because needle holes often present additional points from which bleeding develops later. A simple cut may be treated with pressure dressings left on for four to six days. Often the initial bleeding of such clean lacerations stops fairly soon, only to recur several times over the ensuing days unless pressure is applied constantly. On occasion powdered 'topical thrombin' may improve hæmostasis. An infected wound should be treated similarly and with intensive chemotherapy.

Bruises and *subcutaneous hæmatomas* require no treatment unless severe continued bleeding results. In the latter case, plasma infusions are given; on occasion once or twice daily for three days to tide the child over the acute episode.

Drugs are preferably given by mouth or vein, as hypodermic or intramuscular injections may lead to hæmatomas. Since the tissues of these patients contain a normal amount of thromboplastic substance ('tissue thromboplastin'), venepuncture sites seldom bleed provided adequate pressure is applied immediately and for at least five minutes after withdrawing the needle from the vein. Deep veins, particularly the femoral, should not be used for venepuncture lest the vein wall be lacerated and

massive hæmorrhage result. In one case of attempted femoral puncture in a suspected hæmophilic patient, obstruction to venous return persisted for several days and led to a Volkmann's type of contracture.

It has been stated both by other workers (Birch, 1937), and at times by the children's parents, that increased frequency of hæmorrhage occurs most often during the spring of the year. We have noted that many children pass through 'bleeding phases' when for months on end they appear to bruise more easily and to develop hæmarthroses more frequently. In 35 per cent. of cases such bleeding phases were associated with infections; usually mild upper respiratory ones. A review of 22 patients with repeated admissions to hospital indicated that 10 were admitted more often in the spring of the year, and 12 at other times. It is probable that the increased activity of a growing boy during the spring, and possible changes in the vascular structure of these patients (Pavlovsky, 1947), result in increased bleeding episodes. We have been unable to correlate the occurrence of such ' bleeding phases' with any other events.

REFRACTORY PATIENTS

Infrequently, patients with hæmophilia or with Christmas disease who have received infusions of plasma become refractory to the effect of this replacement therapy (Munro and Jones, 1943; Frommeyer *et al.*, 1950). Three children with classic hæmophilia and one with Christmas disease (4 per cent.) have been resistant for six, five, four and two years, respectively, and have remained so despite the discontinuance of plasma administration for the past eighteen months. All the children, at one time, responded normally to replacement therapy and the cause for their refractoriness is unknown. In one case of Christmas disease the resistance was lost temporarily.

It has been postulated that antibodies to AHF develop in these resistant patients. We have readily demonstrated a potent inhibitor to the action of AHF in their plasma. In contrast to the findings of others (Frommeyer *et al.*, 1950; Craddock and Lawrence, 1947), however, we have been unable to demonstrate a precipitin reaction by layering these plasmas with a solution of Fraction I. Although this anticoagulant activity may be in the gamma globulin fraction (Craddock and Lawrence, 1947), it is altered by clotting, for such activity is lessened in the patient's serum. It has been suggested that massive replacement therapy may overcome the action of this inhibitor (Frommeyer *et al.*, 1950). In one bleeding resistant patient we have been unsuccessful in lowering the clotting time by such treatment since, in such cases, AHF is probably utilized more rapidly than normally.

Twenty-three children have received Fraction I. Two patients with classic hæmophilia who subsequently became resistant are in this group. The resistant patient with Christmas disease received Fraction I which contains no Christmas factor. One child has become refractory who has never been given Fraction I. From this data it seems unlikely that Fraction I is instrumental in causing resistance as has been recently suggested (Alexander, 1955). Many children (62 per cent.) have received over 50 different plasma infusions, some up to 30 litres of plasma, without developing resistance. Why a few of the children of this group (4 per cent.) develop such an

inhibitor against AHF or PTC remains an enigma. We feel that plasma should be administered in limited but adequate amounts and only for severe bleeding episodes. The risk of development of resistance must be balanced by the risk of severe blood loss or development of orthopædic deformity. Large doses of cortisone (300 mg. twice daily) or corticotrophin (75 mg. twice daily) lessen the severity of bleeding clinically, probably through a vasoconstrictor effect on small blood vessels. In our experience, these steroids have no effect upon the clotting mechanism in either the usual or resistant patient. No change in clotting time, prothrombin consumption or the thromboplastin generation test occurred in the four resistant patients who were given cortisone for five days and then a single infusion of fresh plasma (2 to 4 ml. per lb. [4.5 to 9 ml. per kg.]). The care and treatment of these patients is extremely difficult.

PLASMA THROMBOPLASTIN ANTECEDENT DEFICIENCY

The clinical features of patients with plasma thromboplastin antecedent (PTA) deficiency differ from those described, in that manifestations of abnormal bleeding are milder and occur primarily under surgical stress such as dental extraction, tonsillectomy, and abdominal operations and in minor episodes, such as slightly increased tendency to bruise and frequent nose bleeds. Clotting times were normal or slightly prolonged to 18 minutes, prothrombin consumption was normal and all other coagulation studies except the thromboplastin generation test fell within normal control values. In the latter, platelet function was likewise normal and the defect was partially corrected by the substitution of either normal barium sulphate-treated-plasma or normal serum. Characteristic findings such as these have been reported by Rosenthal *et al.* (1953).

VON WILLEBRAND'S DISEASE (PSEUDOHÆMOPHILIA)

The children within this group characteristically have prolonged bleeding-time determinations and prolonged bleeding following lacerations of the mouth in infancy, frequent nose bleeds and hæmorrhage following surgical operations. These abnormalities are due to a combined defect in capillary structure with poor retractability (MacFarlane, 1941) and in thromboplastin generation with varying degrees of AHF deficiency. This latter finding was first reported by Alexander and Goldstein (1953). In our three patients AHF levels range from 20 to 60 per cent. of normal. These levels are probably adequate for normal hæmostasis but, when combined with the vascular defect which appears to be the prime abnormality, may complement the bleeding tendency. In our experience, treatment with cortisone and plasma infusions has halted bleeding within twenty-four to forty-eight hours.

PLASMA THERAPY

It is possible to provide the missing blood component and lower the clotting time of blood in these patients by the intravenous administration of plasma from a normal person. We have used single donor's blood rather than

pooled plasma because of the inherent danger of transmission of serum hepatitis virus. Even though moderate AHF potency may remain in carefully drawn blood for one week when stored at 4°C. (Brinkhous, 1954), it often begins to disappear within several hours. We have not relied on such bank plasma for the treatment of bleeding in patients with classic hæmophilia. AHF, however, remains active for several months in plasma which is freshly frozen at -20°C. or specially dried (dried antihæmophilic plasma, Hyland Laboratories, Pasadena, California). It is essential therefore to separate and freeze the plasma for storage within an hour after the blood has been drawn. As it is required, the material is thawed and administered to the bleeding patient. Plasma, in amounts of 1 to 2 ml. per lb. (2.2 to 4.5 ml. per kg.), is given by intravenous drip every six hours until the bleeding stops. Even this may not be adequate in one-dose amounts, but its effect becomes cumulative and from clinical and laboratory experience such treatment is satisfactory in the patient who is not actively losing blood. In the latter case and in conditions of critical nature, larger amounts have been used and administered continuously, and fresh whole blood may be needed to replace lost red cell mass.

The missing factor in Christmas disease and PTA deficiency remains active in conventionally stored or dried bank plasma for several months. Since this type of plasma is readily available, it is important to differentiate these diseases from classic hæmophilia. Some effect of these substances also remains in the blood of patients for up to ten days. In those with Christmas factor deficiency, we therefore administer bank plasma in doses of 2 ml. per lb. (2.2 to 4.5 ml. per kg.) at twelve to twenty-four hourly intervals.

Plasma should be obtained from a donor of the same ABO and Rh type if possible. After repeated administration, sensitization or plasma reaction may occur if the blood type of the donor is different from that of the recipient. Type O plasma from a 'universal donor' should be neutralized with Witebsky's substances to inactivate some of the saline-active naturally occurring antibodies (1 ml. per 50 ml. of plasma). Plasma is not drawn from persons with a previous history of jaundice, malaria or other diseases transmitted via blood.

In an attempt to prevent hæmorrhagic episodes, prophylactic therapy has been utilized by Alexander and Landweehr (1948) in severe cases (administration of plasma thrice weekly). We have used such a plan occasionally and feel that it is partially successful. The economic problems involved, however, and the possibility of the development of resistance have precluded its use on a large scale and our limited experience does not allow adequate evaluation of this plan.

In small children the amount of bleeding into tissues and joints is often sufficient to produce a rapidly developing anæmia and, at times, shock from blood loss. Fresh whole blood for the patient with classic hæmophilia or von Willebrand's disease, or bank blood for those with Christmas disease or PTA deficiency, must be given to supply red cells in addition to plasma.

We transfuse a child who is bleeding with whole blood when his hæmoglobin drops below 7 grammes.

LOCAL HÆMOSTATIC AGENTS

Oxidized cellulose ('oxycel'), gelatin by-products ('gelfoam') and other materials exert a local hæmostatic effect by hastening coagulation and apparently by-passing the abnormal physiological mechanisms in these children (Seegers and Sharp, 1948). These are clinically effective if placed directly on the bleeding vessel; they are of little use if packed above an already partially formed but poor clot. More potent and physiologically active is commercially prepared bovine thrombin ('topical thrombin') which may be applied locally as a powder or in solution. Our most useful combination of these agents is 'oxycel' soaked in thrombin solution. Fibrin foam and human thrombin are avoided because of the possible transmission of serum hepatitis virus (Porter *et al.*, 1953).

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PURPURA

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By purpura we mean non-traumatic subcutaneous hæmorrhages varying in size from pin-point petechiæ to large ecchymoses an inch or more across. There are two main groups of purpuric disease: (1) those in which abnormalities of the blood are present and abnormalities of the blood vessels are less important; (2) those in which abnormalities of the blood vessels occur, but the blood itself is normal. Humble (1949) has pointed out that the reason why these two groups both produce subcutaneous purpura is that the leak of blood into the tissues occurs at the same point: the junction between the smallest arteriole and the first capillary blood vessel. But otherwise the two groups, usually known as thrombocytopenic purpura and anaphylactoid purpura, present different clinical pictures, pursue a different clinical course, and require different management. The main differences are set out in table 1.

ETIOLOGY OF THROMBOCYTOPENIC PURPURA

Purpura is liable to occur when the blood platelets are depressed below about 40,000 per c.mm. (normal 250,000 per c.mm.). There are two main groups of thrombocytopenic purpura:—

(1) Primary thrombocytopenic purpura in which the cause is still not known.

(2) Secondary thrombocytopenic purpura. In this group the thrombocytopenia and the purpuric rash are caused by: (a) other blood diseases, such as acute leukæmia, aplastic anæmia or reticuloses; or (b) toxic substances, particularly drugs such as phenylbutazone ('butazolidin'), gold, chloramphenicol and sometimes barbiturates. The diuretic, acetazolamide ('diamox'), is the latest addition to the list. Benzol poisoning is given as a cause in all textbooks, but is now very unusual.

The most popular idea is that thrombocytopenic purpura is a form of hypersplenism in which the spleen collects and destroys the circulating platelets more rapidly than usual. The resultant call for more and more platelets is met by hyperplasia of the platelet-forming megakaryocytes in the bone marrow. The good results of removal of the spleen, even though it is rarely more than three times normal size (and therefore not palpably enlarged) confirms this hypothesis. But hypersplenism has never been accepted as a complete answer. Some patients fail to respond to splenectomy when no other primary disease can be found; some patients have thrombocytopenia without hæmorrhages or obvious ill-effect.

Another possible cause was put forward by Ackroyd (1953) who showed that the thrombocytopenic purpura caused by the drug, 'sedormid', was due to the development in the blood of an antibody that destroyed platelets. Thrombocytopenia is often found in acquired hæmolytic anæmia—a disease due to antibody destruction of red blood cells. Techniques were devised

	Thrombocytopenic purpura	Anaphylactoid purpura
Type of rash	Small, reddish-purple spots or large purple areas	Fine, bright-red rash often preceded by swelling, large areas may start as urticaria
Pain in rash	Lesions painless	Lesions painful to pressure, often preceded by itching
Bleeding from mucous membranes	Common from mouth, nose, vagina	Unusual, sometimes in small intestine
Joints	Unaffected	Sometimes painful and swollen
C.N.S. hæmorrhage	Recognized complication	Very rare
Blood count	Platelets low (10,000 to 30,000 per c.mm.)	Platelets normal
Bleeding time	Always prolonged	Sometimes prolonged
Capillary fragility	Hess test positive	Hess test often negative, but Scarborough test positive
Course	Either remits in 3 to 4 weeks or becomes chronic	Recurrent crops of petechiæ for a few weeks, or very chronic course lasting for years
Treatment	Cortisone, prednisolone; or if these fail, splenectomy	Cortisone, prednisolone, or antihistamine drugs
Results of treatment	Very good	Poor, if no spontaneous remission
Occurrence secondary to other blood diseases	Yes	No

TABLE 1.—Differences between thrombocytopenic and anaphylactoid purpura.

for the detection of anti-platelet antibodies in the circulating blood of patients with thrombocytopenic purpura, and at first the results showed that there were such antibodies present in a fair proportion of cases. This suggested that, if antibodies were present, treatment with cortisone would be correct, whereas if they were not present, splenectomy would be indicated. Unfortunately more experience has denied us this attractively simple guide. Patients who have failed to respond to splenectomy may have no

anti-platelet antibodies, and patients who had responded were found to have these antibodies present, even postoperatively. The tests are awkward to carry out and difficult to interpret; antibodies have been detected, by these tests, in the blood of patients who had never had purpura. Consequently, although it is quite likely that platelet antibodies play some part in the etiology of thrombocytopenic purpura, their exact role is as yet uncertain.

DIAGNOSIS OF THROMBOCYTOPENIC PURPURA

The presence of so many potentially serious causes of thrombocytopenia means that before a case can be confidently labelled 'primary', other possible causes must be excluded. Some clues are available from the clinical examination. Severe and obvious anæmia is not often caused by primary purpura; a palpably enlarged spleen is suggestive of leukæmia or reticulosis and is hardly ever found in primary purpura.

The diagnosis, however, is nearly always settled by the laboratory studies of which two are essential: the blood count and examination, and a bone-marrow aspiration biopsy. The blood count will show low platelets and, in some patients with acute leukæmia, the presence of abnormal leucocytes in the peripheral blood will give the diagnosis at once. In other patients the next step is a bone-marrow biopsy; in adults and children over 15 years old, sternal marrow is best; in children under 15 years old I prefer an iliac crest biopsy. The procedure is quite safe and will not cause hæmorrhage provided that pressure is maintained on the puncture site till bleeding really stops, and this may take two minutes or so. Bone-marrow biopsy distinguishes at once the cases which are due to acute leukæmia and aplastic anæmia; in the leukæmias the marrow will contain many abnormal and primitive leucocytes; in aplastic anæmia the marrow will be much less cellular than usual, erythroblasts and granulocytes being relatively few and megakaryocytes absent. In primary thrombocytopenic purpura the bone marrow shows a normoblastic hyperplasia—a response to loss of blood—with often granulocyte activity as well. The megakaryocytes are often increased in number and forms without platelet formation and immature forms may be seen; but neither of these unusual forms needs to be seen to ensure a diagnosis of primary thrombocytopenic purpura. Some megakaryocytes should be found because if they are not, response to treatment is liable to be disappointing.

In every case it is most important to inquire about drugs, and here the general practitioner should always tell the consultant what drugs the patient has been having during the previous three months, not forgetting barbiturates as even phenobarbitone has been known to cause thrombocytopenia, and the new 'tranquillizers' must be regarded as potentially toxic too. No patient with a recent history of taking drugs that can cause thrombocytopenia is treated by splenectomy.

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Occurrence secondary to other blood diseases	Yes	No

TABLE 1.—Differences between thrombocytopenic and anaphylactoid purpura.

for the detection of anti-platelet antibodies in the circulating blood of patients with thrombocytopenic purpura, and at first the results showed that there were such antibodies present in a fair proportion of cases. This suggested that, if antibodies were present, treatment with cortisone would be correct, whereas if they were not present, splenectomy would be indicated. Unfortunately more experience has denied us this attractively simple guide. Patients who have failed to respond to splenectomy may have no

anti-platelet antibodies, and patients who had responded were found to have these antibodies present, even postoperatively. The tests are awkward to carry out and difficult to interpret; antibodies have been detected, by these tests, in the blood of patients who had never had purpura. Consequently, although it is quite likely that platelet antibodies play some part in the etiology of thrombocytopenic purpura, their exact role is as yet uncertain.

DIAGNOSIS OF THROMBOCYTOPENIC PURPURA

The presence of so many potentially serious causes of thrombocytopenia means that before a case can be confidently labelled 'primary', other possible causes must be excluded. Some clues are available from the clinical examination. Severe and obvious anæmia is not often caused by primary purpura; a palpably enlarged spleen is suggestive of leukæmia or reticulosis and is hardly ever found in primary purpura.

The diagnosis, however, is nearly always settled by the laboratory studies of which two are essential: the blood count and examination, and a bone-marrow aspiration biopsy. The blood count will show low platelets and, in some patients with acute leukæmia, the presence of abnormal leucocytes in the peripheral blood will give the diagnosis at once. In other patients the next step is a bone-marrow biopsy; in adults and children over 15 years old, sternal marrow is best; in children under 15 years old I prefer an iliac crest biopsy. The procedure is quite safe and will not cause hæmorrhage provided that pressure is maintained on the puncture site till bleeding really stops, and this may take two minutes or so. Bone-marrow biopsy distinguishes at once the cases which are due to acute leukæmia and aplastic anæmia; in the leukæmias the marrow will contain many abnormal and primitive leucocytes; in aplastic anæmia the marrow will be much less cellular than usual, erythroblasts and granulocytes being relatively few and megakaryocytes absent. In primary thrombocytopenic purpura the bone marrow shows a normoblastic hyperplasia—a response to loss of blood—with often granulocyte activity as well. The megakaryocytes are often increased in number and forms without platelet formation and immature forms may be seen; but neither of these unusual forms needs to be seen to ensure a diagnosis of primary thrombocytopenic purpura. Some megakaryocytes should be found because if they are not, response to treatment is liable to be disappointing.

In every case it is most important to inquire about drugs, and here the general practitioner should always tell the consultant what drugs the patient has been having during the previous three months, not forgetting barbiturates as even phenobarbitone has been known to cause thrombocytopenia, and the new 'tranquillizers' must be regarded as potentially toxic too. No patient with a recent history of taking drugs that can cause thrombocytopenia is treated by splenectomy.

MANAGEMENT OF THROMBOCYTOPENIC PURPURA

The commonest clinical presentation is the appearance of purpura with perhaps a little bleeding from some mucous membranes; the general condition of the patient is good. If the history is short, at most a few weeks, a 'wait and see' policy is best, especially in children and young women up to the age of 25, because spontaneous remission, often permanent, occurs in a fair proportion of patients. But if the purpura is extensive, a course of cortisone, or preferably prednisolone, can be begun at once. Full doses should be used; for adults, 300 mg. a day of cortisone or 40 mg. a day of prednisolone in divided doses; for children, about 200 mg. of cortisone or 30 mg. of prednisolone daily are right. This course should be continued for four weeks, and the position then reviewed. There may have been a complete remission with disappearance of the purpura and a rise of the platelet count to normal levels; in these cases the treatment is stopped and the remission often proves to be permanent.

The patient should be seen at intervals for the next twelve months; if a relapse occurs, splenectomy should be carried out. More commonly the purpura disappears partially or completely, but the platelet count remains low. Steroid treatment should be continued for a further period, up to three months; if the platelet count remains below 40,000 per c.mm., splenectomy should be carefully considered, even though the purpura itself is now minimal. The reason for this is that with so low a platelet count, cerebral hæmorrhage and hæmorrhage elsewhere in the central nervous system is always a possibility. If at any time a patient shows signs of an incipient central nervous system hæmorrhage, splenectomy becomes urgently necessary. Splenectomy should also be considered early in girls approaching the time when the onset of menstruation is expected, and in the young married woman likely to become pregnant. Patients whose thrombocytopenic purpura has appeared during pregnancy have been successfully carried through, but no-one would willingly add this hazard if it could be avoided.

Acute thrombocytopenic purpura is fortunately rare, but is very alarming when it does occur. The patient gives a few days' history of extensive purpura, bleeding from nose and gums, and sometimes hæmaturia; vaginal hæmorrhages may be serious. The patient is very poorly and the hæmoglobin may be low. Once the diagnosis is established the best treatment is blood transfusion followed by prednisolone. Emergency splenectomy used to be recommended for this condition, but has mostly been abandoned because in so many patients the platelets failed to rise for some days, or weeks, after the operation, and then the complication of a bleeding abdominal wound was added to the clinical difficulties.

Present technique is to tide the patient over the acute crisis by transfusion and prednisolone and to carry out splenectomy in a quiet period later on, if the platelets do not rise spontaneously. In this type of case the question of platelet transfusion has to be considered. In blood collected and stored

in the usual way there are few platelets because so many have stuck to the glass, metal and rubber of the collecting apparatus. If all glass surfaces are siliconed, metal surfaces coated with a suitable water-repellent, and silicone rubber or plastic tubing is used for connexions, platelets can be kept intact and are available for transfusion. Transfused platelets survive for four to five days and might seem to be valuable for tiding the patient over an acute crisis. Unfortunately experience has shown that platelet antibodies develop very quickly in the recipient's blood, so that after the first transfusion the survival of platelets is so short that the effort is not worthwhile. There is evidence that 'platelet groups' exist, but no method of determining compatibility has been worked out.

Splenectomy is thus still the recommended treatment for all patients with thrombocytopenic purpura who have failed to show spontaneous remission and have not responded to a 3-month course of cortisone or prednisolone. Splenectomy is successful in most patients. In a group of 81 patients with primary thrombocytopenic purpura seen at Manchester Royal Infirmary, 64 had splenectomy carried out; 47 (74 per cent.) showed the expected rapid rise of platelets to normal, in another nine (14 per cent.) the platelets rose after a delay, so the operation achieved its object in 88 per cent. of patients. It would be satisfying if we could pick out beforehand the 12 per cent. who are the failures; this has proved difficult, but some progress is being made. Most of the failures are women over 45 years old, and it is clear that the chances of a successful response to splenectomy diminish sharply after that age. On histological examination of the spleen a very few have proved to have reticuloses, but such cases are not included in the figures given. Spontaneous recovery occurred in 10 out of these 81 patients (12 per cent.), and this rate is undoubtedly higher in children. So far there is no clear evidence that cortisone has raised the remission rate, but it is known that cortisone, possibly by influencing capillary fragility, has diminished actual bleeding and made splenectomy a relatively easy procedure free from complications.

For the treatment of thrombocytopenia caused by drugs, the object is to tide the patient over until depressed platelet production recovers or until platelet antibodies die away. Splenectomy is not part of the treatment for this group; blood transfusion and cortisone or prednisolone are used.

ANAPHYLACTOID PURPURA

This is the type often given the eponym 'Henoch-Schönlein purpura', and it is the most important non-thrombocytopenic purpura. The clinical picture presents a typical purpuric rash accompanied sometimes by joint swelling, and sometimes by evidence of alimentary-tract hæmorrhage. The rash is at first strikingly bright red and the affected areas are swollen; often the swelling precedes the coloration. The bright red soon changes to purple and then more slowly to brown. Since recurrent crops of purpuric spots

are a feature, most patients present all three stages at the same time. The patient complains that the affected area aches and is tender to the touch, and in the early stages there may be typical irritation at the site. Sometimes ecchymoses, varying from half-an-inch (12.5 mm.) across to large areas several inches across, occur and these are often notably painful. Dependent areas like the legs tend to show the most extensive rash, and pressure points are often marked out by spots. Bleeding from mucous membranes is unusual.

The blood count is always normal and the platelets are normal or slightly depressed. The bleeding time may be somewhat prolonged and the Hess test is sometimes positive. Negative pressure tests, such as that devised by Scarborough (1941), are always positive. In this test a standard negative pressure is applied to a defined area of skin on the forearm for a standard time, and the number of petechiæ that appear is counted; more than one or two indicates increased capillary fragility. The test is also positive in thrombocytopenic purpura.

Anaphylactoid purpura is commonest in children but is quite frequent in young adults; patients over 50 are rarely affected. In children it clears up quickly as a rule, but in adults it often becomes distressingly chronic. In young adults, too, this purpura is often the forerunner, by a few years perhaps, of renal disease and failure. For this reason the urine should always be examined microscopically for the presence of red cells, and renal function checked by carrying out a urea clearance test.

Diagnosis.—This is usually quite clear from the features of the rash and the absence of all changes in the blood count or in tests of blood clotting properties. There are only a few other conditions that need to be considered. The so-called 'senile purpura', which appears to be due to a loss of supporting substance in the subcutaneous tissues, shows fairly large and painless patchy lesions. In scurvy the lesions are also more than petechial and, if the skin is affected, the gums are likely to be affected as well; the skin shows follicular hyperkeratosis and not urticaria. Similarly in purpura accompanying infectious diseases, by the time the purpura appears, the diagnosis is already certain.

Etiology.—This type of purpura is often called 'allergic' purpura, but Ackroyd, in his review, points out that, apart from a few cases in which food allergy was definitely established, the cause of the syndrome is unknown and there is no good evidence for the implication of allergy. He points out that platelets and capillary endothelium are antigenically related. His extensive research into the nature of the purpura caused by 'sedormid' has shown that the thrombocytopenia is due to combination of the drug with platelets to form an antigen which in a few patients stimulates the production of a platelet-destroying antibody. The capillary lesion may also be produced when the drug combines with endothelial cells to form an antigen which reacts with this same antibody. Such a reaction may be the

cause of the non-thrombocytopenic purpuras and work along these lines is proceeding. At Manchester we have seen patients with purpura associated with the presence of an abnormal globulin in the serum and these cases are being investigated to see if they will help in solving this puzzle.

TREATMENT OF ANAPHYLACTOID PURPURA

Patients with Henoch-Schönlein purpura should be tested to see if any allergen, food or inhalant, can be implicated. In the few cases in which this search is rewarded, desensitization can be carried out.

If the urticarial element is prominent, the use of antihistamines is worth exploring: they will often cause the rash to clear, but may not prevent new crops of purpuric spots from appearing. 'Dibistin', a mixture of 50 mg. of antazoline and 25 mg. of tripelennamime, has proved very useful in this purpura; one 75-mg. tablet is given three times daily. Promethazine, 25 mg. three times daily, has also helped in some patients.

The relief of patients by cortisone has been reported quite often in the literature. It is difficult to sort out the therapeutically induced from the spontaneous remission in individual cases, but the balance of evidence is in favour of its value. In my experience cortisone will produce remissions in some chronic cases. The dose should be 300 mg. a day at first, reducing to 200 mg. daily if signs of fluid retention appear. Nowadays, prednisolone is often used instead, the dose being 40 mg. daily at first, dropping to 30 mg. If a remission occurs the cortisone dosage should be dropped in steps to 50 mg. a day for about a month, and then stopped. If after one month's treatment a remission has not appeared, there is no point in continuing the treatment and the dose should be reduced in steps to zero.

Adrenochrome monosemicarbazone ('adrenoxyl') and related compounds have been said to reduce capillary fragility in animals and have therefore been tried in cases of Henoch-Schönlein purpura. In Manchester we have tried this substance, but the results have been disappointing.

Splenectomy should not be carried out in this type of purpura; it brings no relief. Sometimes the operation is followed by a phase of remission, but sooner or later the disease reappears.

Fortunately, in many patients the disease remits after a few weeks or months, but in others it keeps recurring with much pain and disability, and so far we have only symptomatic treatment to offer.

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HÆMOGLOBIN AND ITS ABNORMALITIES

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This article will concern itself with the changes in the nature of hæmoglobin. These do not necessarily cause an anæmia, but they are often of clinical importance, and some are of wider interest from the point of view of biochemistry, biophysics, physiology, genetics and even of anthropology.

THE HÆMOGLOBIN MOLECULE

Hæmoglobin is a conjugated protein in which the hæm, a ferroporphyrin, is the prosthetic group. Four hæms are attached to the protein moiety—globin. Hæmoglobin is by no means confined to the higher animals, or even to the animal kingdom. It has been found in protozoa, in the roots of leguminous plants, in yeasts and in moulds (Keilin, 1953). The hæm is identical in all species. The molecular weight of the globin varies in invertebrates, but in vertebrates it is uniformly 68,000. The nature of the globin, however, varies from animal to animal and is different in the multiple hæmoglobins of a single species.

CHANGES IN THE HÆM

The physiological function of hæmoglobin is based upon its loose combination with oxygen. Oxyhæmoglobin loses the oxygen when the partial pressure of the gas falls, and it becomes re-oxygenated when the oxygen pressure is restored. This reversible oxygenation does not involve the iron atoms which are in the divalent ferrous form. When the ferrous hæmoglobin becomes oxidized to ferric hæmoglobin—methæmoglobin—the curve of dissociation is changed. It becomes more difficult to exchange the loosely bound molecular oxygen. Similarly, if the ferrous hæmoglobin combines with carbon monoxide instead of with oxygen or carbon dioxide, carboxyhæmoglobin results with a dissociation curve which does not allow reversible oxygenation to proceed easily.

Methæmoglobinæmia.—There is a steady formation of methæmoglobin in the red cells but enough reduced coenzyme I (diphosphopyridine nucleotide) is formed during glucolysis to reduce the ferric protein as rapidly as it is formed. Methæmoglobinæmia may occur as a result of the toxic effects of drugs such as phenacetin, acetanilide and antipyrin. In these cases the methæmoglobin disappears within a few days of withdrawing the drug. There is a rare condition—only a few dozen cases have been described—in which methæmoglobin is congenital and where it persists in the absence

of specific treatment (see Barcroft *et al.*, 1945). The cause is an inherited deficiency of a flavoprotein (coenzyme factor I) which acts as a catalyst in the reduction of methæmoglobin by coenzyme I (Gibson, 1948).

Although methæmoglobinæmia may cause a marked cyanosis, most patients suffer from no physical disability. Methæmoglobinæmia should be suspected whenever there is a deep cyanosis without dyspnœa. In some of the congenital conditions, however, methæmoglobin may form nearly half of the red cell pigment, and there may be dyspnœa on effort. Treatment with ascorbic acid by mouth or by injection will reduce the cyanosis dramatically, and this can be used as a diagnostic test. Methylene blue given by mouth will act even more rapidly and completely. It couples the methæmoglobin with reducing enzymes which otherwise have no effect, or act only at a slow rate.

There has also been described one family with hereditary methæmoglobinæmia where the globin moiety was abnormal, and where treatment with methylene blue or with ascorbic acid failed to bring about a reduction of the ferric ion (Hörlein and Weber, 1948). On separation of the hæm and globin and recombination with those of normal persons it was possible to show that the globin of the members of the affected family was incapable of forming a ferrous protein.

Sulphæmoglobinæmia.—When methæmoglobinæmia is associated with prolonged or excessive ingestion of drugs, and particularly if there is also a history of constipation, varying proportions of the pigment will be further converted into sulphæmoglobin. In practice sulphæmoglobinæmia is the more frequently encountered condition. Sulphæmoglobin cannot be converted into normal hæmoglobin by reducing agents. Excessive putrefaction in the intestine can cause an increase in hydrogen sulphide, and it has been demonstrated experimentally that hydrogen sulphide can react with hæmoglobin in the presence of oxygen to form sulphæmoglobin, and that this process is accelerated when derivatives of aniline are present (Archer and Discombe, 1937). The exact nature of sulphæmoglobin is still unknown. Presumably a nitrogen bonded to the iron atom is replaced by sulphur. As in drug-induced methæmoglobinæmia, so in sulphæmoglobinæmia the treatment consists primarily in stoppage of the offending therapeutic agent, but it is also worth avoiding the accumulation of food residues in the colon.

ABNORMAL SYNTHESIS OF THE GLOBIN

In contrast to most of the conditions in which hæmoglobin is abnormal as a result of changes in the hæm, the known abnormalities of globin synthesis are all permanent and inherited. The diseases caused by such abnormalities have been called hæmoglobinopathies. They are characterized either by a block in the production of normal hæmoglobin or by its replacement by one of its variants, or by a combination of these two. All hæmoglobinopathies show an increased rate of hæmolysis. It is now known that a variation in hæmoglobin synthesis may not invariably cause a hæmoglobinopathy, particularly in heterozygotes for an abnormal gene. To include all conditions

it might be more appropriate to call them hæmoglobinoses (table I), some of which would then be hæmoglobinopathies.

	Hæmoglobin F	Other Hæmoglobins
Sickle-cell anæmias (S.C.A.)		
Classical S.C.A.	Usually present	S
Microdrepanocytic disease	Usually present	S + A A may be absent
Hb. C S.C.A.	Usually present	S + C
Hb. D S.C.A.	Up to now always found	S + D
Thalassæmias (Thal)		
Thal major (homozygous)	Can vary from nil to 90 per cent., usually 10 to 20 per cent.	A with raised proportion of A_2
Thal minor (heterozygous)	Usually present, but more often absent than in Thal major. Rarely 10 per cent.	A with raised proportion of A_2
Hb. C thalassæmia	Present as in Thal minor	C + A
Hb. D thalassæmia (one case)	4 per cent.	D + possibly trace of A
Hb. E thalassæmia	20 to 40 per cent.	E
Hb. H thalassæmia	Present	A + H
Non-sickling, non-thalassæmic diseases		
Hb. C disease	Traces present, but not regularly	C
Hb. D disease (not proven by family studies)	Absent	D
Hb. E disease	Absent or traces	E
Hb. M disease	?	A + M ?
Conditions not known to give rise to diseases (traits)		
Sickle-cell trait	Absent	A + S
Hb. C trait	Absent	A + C
Hb. D trait	Absent	A + D
Hb. E trait	Absent	A + E
Hb. G trait	Absent	A + G
Homozygous G (one case only)	Absent	G
Hb. H trait (presumed in parents of Hb. H thalassæmia)	Absent	A
Hb. I trait	Absent	A + I
Hb. J trait	Absent	J + A
Hb. K trait	Absent	A + K

TABLE I.—The Hæmoglobinoses.

The abnormalities of hæmoglobin synthesis can be divided into three groups:—

(1) Conditions in which there is an inherited defect in the production of normal hæmoglobin not associated with a deficiency of hæmopoietic substances. Thalassæmia is an example.

(2) Conditions in which normal hæmoglobin is replaced by one or two abnormal variants. Some of these variants have been proved to be allelomorphs of normal hæmoglobin. Sickle-cell anæmia is an example.

(3) Combinations of 1 and 2. Sickle-cell thalassæmia (microdrepanocytic disease) is an example.

THE NORMAL HÆMOGLOBINS

The two physiological hæmoglobins are adult hæmoglobin (hæmoglobin A) and fœtal hæmoglobin (hæmoglobin F). Both are under an independent genetical control (for an exhaustive review of hæmoglobin F see Betke, 1954). At birth more than half of the hæmoglobin is in the F form, its concentration falls steadily until, at the age of 4 to 6 months, none can be discovered by the usual chemical methods. Hæmoglobin F was discovered nearly a hundred years ago when it was noted that the red-cell pigment of the new-born infant, unlike that of the adult, was not denatured by alkaline reagents. To this day most laboratories measure the concentration of hæmoglobin F by determining the percentage of 'alkali-resistant hæmoglobin'.

The two hæmoglobins differ in their oxygen dissociation, the curve of hæmoglobin F being to the left of that for hæmoglobin A. In the ultra-violet spectrum the position of the tryptophane fine-structure band differs by 12 Å. There are slight differences in the isoelectric point, and hence in electrophoretic mobility, and also in immunological specificity.

Hæmoglobin F cannot be called an abnormal hæmoglobin but its presence after the age of 6 months indicates that there is some early impediment of hæmoglobin A production. The inherited hæmoglobinopathies begin to cause anæmia within a few months after birth, at a time when hæmoglobin F is still produced, and it seems that anæmia in early infancy is associated with a persistence of the fœtal pigment beyond the age at which it is normally found. Thus, the finding of hæmoglobin F is almost a part of the diagnostic procedure for thalassæmia and sickle-cell anæmia. The early anæmia associated with a persistence of hæmoglobin F need not necessarily be due to an intrinsic defect of hæmoglobin A formation (Singer *et al.*, 1951; Beaven and White, 1953; Chernoff, 1955). The phenomenon is seen occasionally in spherocytic anæmia where the abnormality is one of the red-cell shape leading to an increased elimination of red cells by the spleen, in leukæmia, in malnutrition, and even in cyanotic conditions such as congenital heart disease where there is only a relative lack of hæmoglobin and no anæmia.

THALASSÆMIA

In thalassæmia, also known as Cooley's anæmia, microcythæmia, Mediterranean anæmia and hereditary leptocytosis, there is interference with the expression of the gene responsible for hæmoglobin A formation. Although the term thalassæmia was introduced to indicate the frequency of the condition in Italians and Greeks, the gene is now known to occur in many different races. Thalassæmia was the first hæmoglobinopathy for which a familial incidence was established, and in which it was shown that the homozygotes were more severely affected (Angelini, 1937; Caminopetros, 1938; Gatto, 1941; Dameshek, 1943; Valentine and Neel, 1944).

Thalassæmia major.—The homozygous condition, thalassæmia major, results in severe anæmia; death usually intervenes before adolescence. The clinical picture and the laboratory findings show similarity with those seen in iron-deficiency anæmia. The cells are hypochromic and microcytic. There is much anisocytosis, and poikilocytes and target cells ('Mexican hat cells') are numerous. Nucleated red cells are present when the condition is severe. In contrast to iron-deficiency anæmia the microcytosis tends to be due more to flatness of the cells than to a decrease in their diameter. As the resistance of a cell to hydration is largely a measure of the difference between the volume of the red cell and that of a sphere of equal surface (Castle and Daland, 1937), it is not surprising that the flattened cells of thalassæmia show a greatly decreased osmotic fragility: some remain intact when suspended in distilled water. It is often difficult to distinguish thalassæmia from iron-deficiency anæmia; in both the defect is one of hæmoglobin synthesis rather than of cell maturation. Although there is an increased rate of hæmolysis in thalassæmia, serum bilirubin level is usually not raised. In iron-deficiency the hæmoglobin A formation is inhibited by the difficulty of finding enough iron to produce an adequate amount of hæm, hence the anæmia improves with iron therapy. In thalassæmia the materials for hæmoglobin A production are all present, but the erythroblast cannot make use of them. Iron therapy is useless, and there is the apparent paradox of a hypochromic microcytic anæmia with copious iron stores in the bone marrow and a high serum iron level. Fœtal hæmoglobin is almost invariably present—another difference from iron-deficiency anæmia (Liquori, 1951). There is no correlation between the amount of hæmoglobin F and the severity of the anæmia.

Thalassæmia minor.—The heterozygous thalassæmia is usually less severe than thalassæmia major. As a rule, interference with the gene responsible for hæmoglobin A formation is less marked, and the condition has therefore been called thalassæmia minor. In some instances only will the penetrance of the single thalassæmia gene be so powerful that the term 'minor' becomes a misnomer. Family studies may then be required to prove that the patient is not a homozygote. The majority of thalassæmia heterozygotes show some signs of abnormal hæmoglobin synthesis, but the anæmia is only moderate or may be entirely absent. The blood film shows hypochromia, poikilocytosis and leptocytosis, and the decrease in mean corpuscular thickness can either be measured directly or can be inferred from a raised resistance of the cells against lysis by hypotonic saline solutions. Some hæmoglobin F is usually present.

In some thalassæmics the penetrance of the single gene can be so poor and cause so little disturbance of hæmopoiesis that the abnormal genotype can only be ascertained from a family study.

The reason for the wide variation of penetrance is unknown. It has been suggested that there might exist different thalassæmia genes. There is no doubt that there are some notable differences between the blood picture of thalassæmia minor in Italy

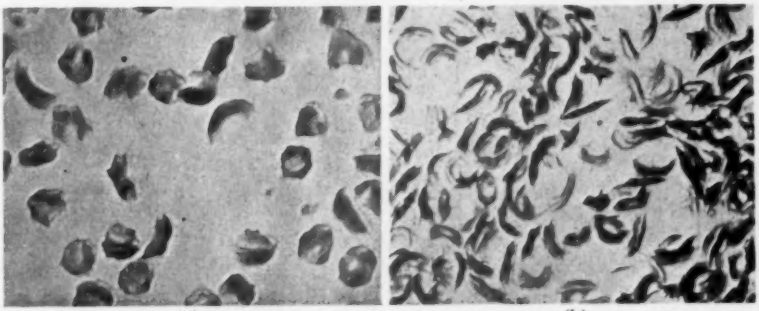
and of the few instances of the condition seen recently in the Gold Coast (Edington and Lehmann, 1955). Widely differing degrees of severity may be seen in the thalassæmic offspring of the same parents.

Hæmoglobin A_2—the Kunkel phenomenon.—Careful analysis of normal hæmoglobin of adults has demonstrated that it consists of at least two, possibly three, fractions. One of them, hæmoglobin A_2, resembles in its electrophoretic mobility the abnormal hæmoglobin E (Kunkel and Wallenius, 1955). Normally not more than 3 per cent. of hæmoglobin A is in the A_2 form, but A_2 is present in concentrations up to 15 per cent. in a majority of thalassæmics. Examination for a raised proportion of hæmoglobin A_2 may become a useful tool in the diagnosis of thalassæmia.

In thalassæmia the amount of circulating hæmoglobin A is low because of the interference with the synthesis of the normal pigment. In the other hæmoglobinoses an abnormal variant replaces it to a varying extent.

THE SICKLE-CELL AND ITS HÆMOGLOBIN

The first variant of adult hæmoglobin to be discovered was the sickle-cell hæmoglobin (hæmoglobin S). It is of interest to note that forty years elapsed



(a) (b)

FIG. 1.—Sickle cells: (a) Sickle cells shortly after a reducing agent has been added; the early stages of sickling can be noted. (× 750.)
(b) A preparation in which sickling is nearly complete. (× 500.)

between Herrick's (1910) first description of 'peculiar elongated and sickle-shaped red corpuscles in a case of severe anæmia' (fig. 1) and the fundamental announcement by Pauling and his colleagues (1949) that sickle-cell anæmia was a molecular disease due to an abnormal hæmoglobin.

Most of the techniques which up to then had been employed to differentiate between the adult and fœtal pigments would have failed to recognize the hæmoglobins discovered since 1949. Hæmoglobin F is so far unique in being resistant to alkali, in possessing a different ultra-violet spectrum and in showing immunological specificity. On the other hand, hæmoglobins A and F differ little on electrophoresis, and this was the technique by which hæmoglobin S was discovered (fig. 2).

In this technique proteins are dissolved in a buffer solution and an electric current is passed. The charge of the protein and the speed at which it will migrate towards the negative or the positive pole depend upon the difference between the pH of the buffer and the pH at which the protein is isoelectric. If both are the

same the protein will be neutral and remain stationary. If the pH of the buffer is on the acid (negative) side of the isoelectric point the protein will carry a positive charge and will move towards the cathode, and if the pH of the buffer is on the alkaline (positive) side, the protein will behave as an anion and move towards the anode.

The isoelectric points of hæmoglobins A and F are very similar (6.9 and 6.9 to 7 respectively), hence electrophoresis has not been an efficient method of separation. The isoelectric point of hæmoglobin S is 7.1, hence once electrophoresis was applied a separation was easily achieved.

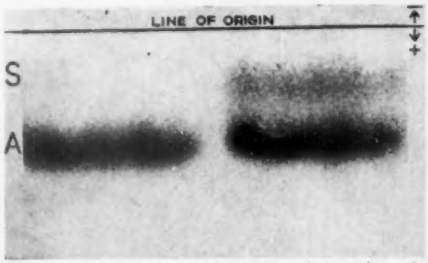


FIG. 2.—Comparison by paper electrophoresis (pH 8.6) of normal hæmoglobin (A) with that of sickle-cell trait carrier (A + S). The normal hæmoglobin moves as a single band, whereas the abnormal hæmoglobin separates into two components, one identical with A, and one moving more slowly—hæmoglobin S.

The first sickle-cell anæmia patient seen was a West-Indian Negro who was in Chicago as a student. Subsequent observations were also made on Negroes (fig. 3). It was then noted that some Negroes had erythrocytes which appeared perfectly normal *in vivo*, but which could be induced to sickle *in vitro*. Hahn and Gillespie (1927) reported that sickling only occurs with low oxygen tensions and that sickled cells revert to the normal shape when they are exposed to sufficient oxygen. A slightly acid pH seemed to favour sickling. The sickling phenomenon was found to be familial, and the mode of inheritance that of a single Mendelian dominant (Emmel, 1917; Taliaferro and Huck, 1923). At first it was assumed that the same gene produced in some persons an asymptomatic condition—the sickling trait, and in others was responsible for a severe disorder—sickle-cell anæmia. Neel suggested, in 1947, that there might be an alternative hypothesis similar to that which differentiated between thalassæmia major and thalassæmia minor as homozygous and heterozygous states. In 1949, he presented convincing evidence, and simultaneously and independently the same hypothesis

FIG. 3.—Photograph of child with sickle-cell anæmia. Note bossing of skull. (*By courtesy of Dr. P. W. Hutton, Uganda.*)

was advanced by Beet (1949). Dramatic support was given to the genetic theory when Pauling discovered the sickle-cell hæmoglobin, and when it was shown that patients with sickle-cell anæmia (homozygotes) had no normal hæmoglobin, but that sickle-cell trait carriers (heterozygotes) possessed both the abnormal and the normal pigment.

In most cases of sickle-cell anæmia not all the hæmoglobin is hæmoglobin S; traces of hæmoglobin F are present (Singer *et al.*, 1951), and the finding or the absence of hæmoglobin F in a sickler is of help when a diagnosis has to be made without electrophoresis.

Direct evidence for the physical base of the sickling process was obtained by solubility studies.

Harris (1950) found that the de-oxygenation of concentrated solutions of hæmoglobin S resulted in a semi-solid gel. Under the microscope, tactoids 1 to 15 μ long could be observed which were remarkably similar in shape to sickled cells. On re-oxygenation the tactoids disappeared but they formed again when the oxygen was removed. Perutz and his colleagues (1950, 1951) found that reduced hæmoglobin S was much less soluble than reduced hæmoglobin A. Oxygenated hæmoglobins A and S have the same solubility, but, whereas on de-oxygenation the solubility of hæmoglobin A falls by one half, that of hæmoglobin is only 2 per cent. of the solubility of the oxygenated pigment (*see also* Itano, 1953). When cells containing sickle-cell hæmoglobin are reduced, intracellular tactoids are formed. These formations stretch the cell envelope and produce the bizarre shape of the sickle-cell.

There had already been fundamental clinical observations by Diggs and his colleagues (1933), by which the anæmia had been separated from the trait, and careful observations by Sherman (1940) had shown that the two conditions differed in their tendency to form sickle cells. Sickle-cell anæmia is hæmolytic in nature with a reduction in survival time of the erythrocytes to two to eight weeks instead of the normal life span of six months. Trait cells survive normally even when they are transfused into a sickle-cell anæmia patient (Singer *et al.*, 1948; Callender *et al.*, 1949). All these observations can now be explained on the basis of the abnormal hæmoglobin content of the erythrocytes. The greater the tendency to sickle the more likely are hæmolytic crises to arise, and the more often will be seen the infarctive conditions which are typical for sickle-cell anæmia. As intravascular sickling may cause blockage of small vessels in all parts of the body, sickle-cell anæmia can present as a hæmaturia or as an acute abdominal emergency, as pneumonia, heart disease or with neurological manifestations. Arthralgia is frequent, and leg ulcers are common; these, however, are also a feature of the non-infarctive thalassæmia major and of hereditary spherocytosis. Harris and his colleagues (1956) have explained all the features of sickle-cell anæmia on a biophysical basis: 'The sickled erythrocyte is essentially a membrane-covered tactoid'. Because of the abnormal shape of the red cells there is an increase in the viscosity of the blood, and stasis results. The fall in pH and the continued uptake of oxygen by the tissues will cause more sickling. With a greater number of sickled cells the viscosity will increase further and the stasis will be prolonged. Sickled cells are more fragile than cells of normal configuration and when the erythrocytes are

released after stasis, a certain proportion have been fixed in the sickled form and have therefore become more fragile. Thus the abnormalities of the erythrocytes are responsible not only for the various occlusive conditions and venous thromboses that underlie the tissue changes but also for the hæmolytic anæmia.

Whether the heterozygous condition is always symptomless has been doubted. Splenic infarction associated with high-altitude flying has repeatedly been reported in non-anæmic sicklers. Conn (1954) has recently summarized nine instances in five of which the hæmoglobin level was above 14 g. per cent. There are numerous other examples which have not been published. Severe unexplained hæmaturia has been seen in a number of patients in whom the sickling condition was proved to be the trait (Goodwin *et al.*, 1950; Chernoff, 1955).

Keitel *et al.* (1956) have found that sickle-cell anæmia patients above the age of 7 years are unable to produce urine with a concentration above 500 milliosmol. Younger patients or adult patients who have been transfused with normal blood may concentrate their urine above this level. Of 26 sickle-cell trait carriers only eight achieved a urine concentration within the 95 per cent. range of normal. These authors suggest that this hyposthenuria results either from renal damage due to intravascular sickling—the kidney uses a great deal of oxygen—or that sickle-cell hæmoglobin interferes with the tubular function. It can be assumed that hæmoglobin S, like normal hæmoglobin, is reabsorbed by the tubular cells from the tubular urine. If the hyposthenuria of sicklers was caused by an effect of hæmoglobin S on the tubules a hitherto unknown process would have to be invoked. Simple intracellular precipitation of hæmoglobin S is unlikely at dilutions which must be well under 1 per cent.

NON-SICKLING HÆMOGLOBIN VARIANTS

On the whole, the recognition of hæmoglobin S, the studies of its biochemical and physical properties, and the examination of individual patients and their families went far to support the genetical theory which postulated that sickle-cell anæmia was the disease of the homozygote. Departures from this hypothesis led to the discovery of other abnormal hæmoglobins. For an exhaustive description the reader will turn with advantage to the following review articles: Singer, 1955; Chernoff, 1955; Zuelzer *et al.*, 1956; Itano *et al.*, 1956; Lie-Injo Luan Eng, 1956.

In addition to normal adult, fœtal and sickle-cell hæmoglobin, nine other human hæmoglobins have been recognized up to date. In 1953, a group of interested workers was called together by the United States Public Health Service to meet under the chairmanship of J. V. Neel and to decide on a standard system of nomenclature. The following system was proposed and has been universally accepted ('Statement', 1953):—

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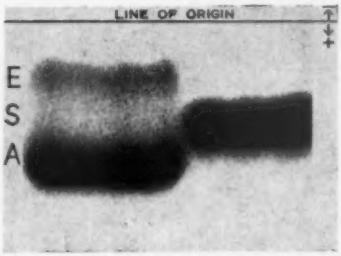

FIG. 4.—Comparison by paper electrophoresis (pH 8.6) of the hæmoglobin of a patient with sickle-cell anæmia, with that of a hæmoglobin E trait carrier. Note that at pH 8.6 S moves more slowly than A and faster than E.

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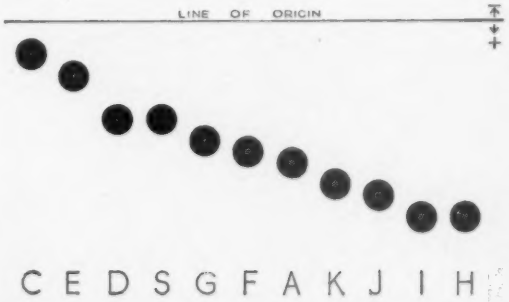

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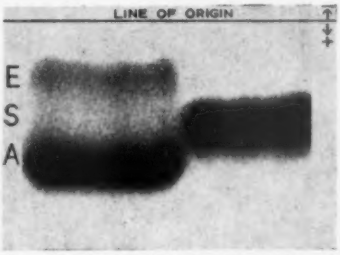

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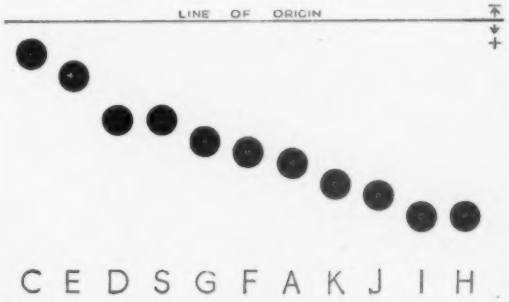

FIG. 5.—Scheme of mobility of the varieties of human hæmoglobin on electrophoresis at pH 8.6.

Hæmoglobins A, S, C, D, E, G, H, J and I have all been found to show no difference in their visible and ultra-violet spectrum, or in their resistance to alkaline denaturation.

The most important differences between the hæmoglobins from the laboratory point of view are in their behaviour on electrophoresis (fig. 4).

In 1953, Spaet showed that hæmoglobin variants could be separated by filter paper electrophoresis. Starch plates can be used instead of filter paper (Kunkel and Wallenius, 1955).

Paper electrophoresis is usually carried out at pH 8.6 and at this pH good resolution is achieved for most mixtures (fig. 5). Hæmoglobins S and D have identical electrophoretic properties and cannot be told apart by this technique. Reduced hæmoglobin D, however, is not as insoluble as reduced hæmoglobin S, hence it does not cause sickling. A sickle-cell test on the intact cells and the measurement of the solubility of the de-oxygenated form will distinguish between the two hæmoglobins. There is some difficulty in differentiating at pH 8.6 between hæmoglobins C and E, J and K, and H and I respectively. Further examination at pH 6.5 then becomes necessary. At that pH hæmoglobin C has the greatest mobility, but E is found between the positions of A and S. At pH 6.5 hæmoglobin H is still an anion and, unlike all the other hæmoglobins, will move towards the positive pole. Hæmoglobin K moves just a little more slowly than hæmoglobin J at pH 8.6, and a little faster than K at pH 6.5.

TRAITS AND DISEASES

Except for an occasional nephropathy or splenic infarct noted in AS heterozygotes, no abnormalities have been recorded in people heterozygous for hæmoglobin A and one of its variants—unless they carry in addition a gene for thalassæmia. The most severely pathological condition is the SS state. Hæmoglobin C disease, hæmoglobin D disease and hæmoglobin E disease are much less serious and seem usually to be compatible with a survival into adult life. No abnormality was noted in the one homozygote for hæmoglobin G who has so far been examined. The disease states are associated with an increased rate of hæmolysis. Whether this will result in anæmia, and whether this anæmia will be moderate or severe, will depend upon the degree of compensation achieved by a higher activity of the bone marrow. Target cells (fig. 6) are commonly seen in the hæmoglobinopathies and the osmotic fragility is decreased. They all show a resemblance to thalassæmia, but an analysis of the hæmoglobin will differentiate the various syndromes.

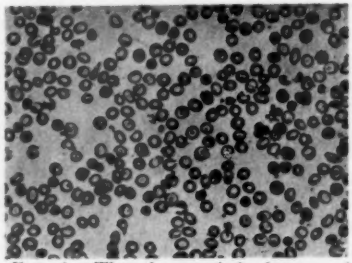

FIG. 6.—The characteristic feature of the non-sickling hæmoglobinopathies is a high proportion of target cells. (× 250.)

Schwartz and Hartz (1955) have re-examined families in whom, in 1949, a diagnosis of thalassæmia had been made on clinical grounds and because of the thalassæmia-like appearance of the blood smear. They found that in some of the patients the underlying cause of the hæmoglobinopathy was in fact hæmoglobin C and not thalassæmia.

Two conditions are known in which there is heterozygosis for two

abnormal hæmoglobins: hæmoglobin C—sickle-cell anæmia (SC), and hæmoglobin D—sickle-cell anæmia (SD). In each case an atypical course of sickle-cell anæmia led to their discovery. The clinical state is most variable. Completely asymptomatic 'patients' have been described who would have been unnoticed had not the relatives of a more affected person been examined. On the other hand, there may be serious debility comparable in severity to homozygous sickle-cell anæmia. In addition, whereas sickle-cell anæmia does not show much fluctuation of severity, except for the occasional crises, SC disease at least, and to a lesser extent SD disease, may vary considerably in their symptoms when the same patient is seen at intervals. Homozygous sickle-cell anæmia usually causes early death; a heterozygous condition should therefore be suspected when an adult person suffers from sickle-cell anæmia.

COMBINATION OF ABNORMAL HÆMOGLOBIN WITH THALASSÆMIA

Before the abnormal hæmoglobins had been discovered an important observation had been made by Silvestroni and Bianco (1955). They had noted that in some patients both sickling and thalassæmia contributed to the blood picture of patients suffering from a condition which was otherwise indistinguishable from sickle-cell anæmia. They named the syndrome microdrepanocytic disease (microcythæmia plus drepanocytosis). Examination of families in which one parent of a child with sickle-cell anæmia failed to sickle led to the discovery of microdrepanocytic disease with increasing frequency. The usual mode of inheritance is that one parent contributes a thalassæmia gene, and the other a gene for hæmoglobin S. But as the two factors are under an independent genetical control, it is possible for a parent with microdrepanocytic disease to transmit both abnormalities. As the thalassæmia gene causes a blockage in the synthesis of hæmoglobin A, the patient, though heterozygous for hæmoglobins A and S, will possess a greater proportion of the abnormal hæmoglobin than is found in the non-thalassæmic sickle-cell trait carrier. Hæmoglobin F is usually present, but as it is also found in homozygous sickle-cell anæmia its demonstration cannot contribute to the diagnosis. The majority of patients with microdrepanocytic disease present with a moderately severe sickle-cell anæmia, but there is a variability in the condition resembling that seen in thalassæmia minor. The penetrance of the thalassæmia gene may range from nil to one resulting in complete suppression of hæmoglobin A production. In the extreme cases family studies are required to differentiate the microdrepanocytic condition from sickle-cell trait or from sickle-cell anæmia.

Thalassæmia has also been seen in combination with hæmoglobins C, D, E and H.

Hæmoglobin E thalassæmia is often found in South-East Asia, although it was first discovered in a half East Indian child in the United States (Itano *et al.*, 1956).

The most important studies were made in Siam (Chernoff, 1955) and subsequent observations were made in Indonesia, Burma, and Bengal. In hæmoglobin E thalassæmia no hæmoglobin A is found, and its place is taken by 20 to 40 per cent. of hæmoglobin F. Complete absence of hæmoglobin A has also been noted in some patients with hæmoglobin C thalassæmia, and the one patient with hæmoglobin D thalassæmia so far described showed no hæmoglobin A on paper electrophoresis, but zone electrophoresis revealed a trace (Hynes and Lehmann, 1956).

A somewhat complicated chain of inhibition of gene penetrance seems to exist in the case of hæmoglobin H (Motulsky, 1956). All the AH phenotypes seen so far were double-heterozygotes for thalassæmia and hæmoglobins A and H respectively. Where family studies have been possible it has always been found that one of the parents of the propositus was a heterozygote for thalassæmia, but that neither parent possessed the abnormal hæmoglobin. The available evidence suggests that the gene for hæmoglobin H shows no penetrance in the AH heterozygote unless there is a partial block of hæmoglobin A synthesis by thalassæmia.

RACIAL DIFFERENCES IN THE DISTRIBUTION OF THE HÆMOGLOBINOSES

The frequencies of the genes for thalassæmia and for the abnormal hæmoglobins differ among the human races (fig. 7) (Lehmann, 1954, 1956). When sickling was first discovered the phenomenon seemed to be restricted to Negroes. A few 'white' sicklers were found, but Negro ancestry could not be ruled out. As one might expect the sickle-cell gene is present in tropical Africa, but it is not equally distributed among the African races. The highest incidences occur in that part of the continent which lies south of the Sahara desert and north of the Zambesi river. Even within this tropical belt some races such as the Hamitomorphs of East Africa are virtually free from sickle cells. Sickling is found occasionally in Mediterranean populations where one might assume that the gene has been imported with African slaves in Roman times. A recent introduction by Turkish soldiers seems to be established for Thrace. In the Middle East, sickling is found in a number of Arab communities; some genes have undoubtedly been introduced with East African slaves, but it is possible that others have been inherited from the pre-semitic populations of Arabia. Of special interest is the presence of sickling in some Veddoid tribes of Southern India. The Dravidian and Aryan populations there show no sickle cells, and it has been suggested that Africa and India received the gene from the same source—the Middle East. It is from there that it is assumed that Veddoid populations moved in prehistoric times southwards both into Africa and into India.

Hæmoglobin C is present at high frequency in West Africa, and within West Africa the highest incidences have been noted for the Northern Gold Coast. Hæmoglobin D has been found in 3 per cent. of North-West Indians, and in about 1 per cent. of Gujeratis who derive from the region of Bombay. Numerous other Indian populations have been examined but so far the only other finding is that of hæmoglobin E at low frequency in Bengalis. Hæmoglobin E is present at a frequency of more than 10 per cent. in Burmese, Siamese and Eastern Malayans. In Western Malaya, E is less often found, presumably because of the admixture of Indonesian immigrants who have come across the Straits of Malacca. Hæmoglobin E has also been found at

lower frequencies in Indonesia, Sarawak, Cambodia, and in Bengal and Ceylon, although in Ceylon it was present only in the aboriginal Veddas and not in the Singhalese.

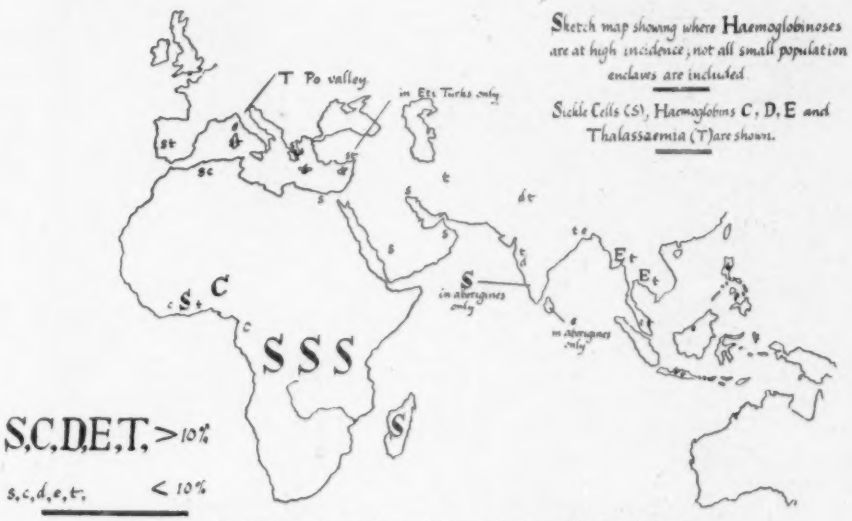
Sketch map showing where Haemoglobinoses are at high incidence; not all small population enclaves are included.
Sickle Cells (S), Haemoglobins C, D, E and Thalassaemia (T) are shown.
T Po valley
in Et Turks only
S
in aborigines only
S S S
S,C,D,E,T, >10%
s,c,d,e,t, <10%

FIG. 7.—Sketch map showing world distribution of hæmoglobinoses.

The other hæmoglobins have so far not been found at regular frequencies but it seems that G, J, and K may exist at low incidence in West Africa, and although H was found in one Greek family and in one Arab from the Jordan, the other observations were made on Chinese, Filipinos and on one Malay.

Of all the abnormalities of hæmoglobin synthesis thalassæmia shows the most widespread distribution. At first discovered in Southern Europeans —and therefore called thalassæmia or Mediterranean anæmia—it has by now been found not only in nearly all the countries bordering on the Mediterranean but also in the Middle East, Pakistan, India, Burma, Thailand, Malaya, Indonesia, the Philippines and Cambodia. The condition has also been seen, though only occasionally, in Chinese and in American Negroes. A few instances have been seen in tropical Africa, and in Central and Western Europe.

SICKLING AND MALARIA

Many genes for thalassæmia and for abnormal hæmoglobins must be lost in every generation when hæmoglobinopathies cause death before the age of puberty. In particular, children with homozygous sickle-cell anæmia or with thalassæmia major rarely survive to become adults, and even then it is unlikely that they can have children. A successful outcome of pregnancy is

virtually unknown in these conditions. Yet in spite of their selective disadvantage, the genes responsible for the hæmoglobinopathies are at high frequencies in many parts of the world. Although a racially determined increase in the mutation rate for these genes has been envisaged, no support for this hypothesis could be found when families were examined on a large scale (Vandepitte *et al.*, 1955). An alternative explanation is a balanced polymorphism, where heterozygotes for the normal and the abnormal genes are more viable than both homozygotes (Neel, 1953). That the advantage for the heterozygote might be a greater resistance to malaria was a hypothesis adumbrated for sickling by Beet (1946), but was stated clearly first by Haldane (1949) who used thalassæmia as his example. A good deal has been written about the relation between sickling and malaria, much of it controversial (Edington and Lehmann, 1956).

The postulate is that AS heterozygotes die less often from malaria than normal homozygotes (AA). The proportionally greater loss of A genes would then balance the loss of S genes from sickle-cell anæmia. The AS heterozygote would possess enough hæmoglobin S to make his red cells unpalatable to the malaria parasite which is highly specialized in its metabolism to utilize hæmoglobin A, but on the other hand the hæmoglobin S content of the cells will be too low to cause sickle-cell anæmia. By directing attention to *P. falciparum* rather than to the malarial parasites in general Allison (1954) provided a sound experimental basis for further investigations. He was the first to produce concrete evidence in favour of protection of sicklers against malaria. This particular evidence could not be confirmed, but Allison's conclusions have been fully vindicated by Raper (1955, 1956), who found that there was no difference in the parasite rate between sicklers and non-sicklers, but that sicklers once infected showed a significantly lower density of *P. falciparum* in their blood smears. This applied only to children under the age of 2: i.e. before acquired immunity became established. After that age this secondary immunity protects sickler and non-sickler alike. As the severity of *P. falciparum* infection determines the malarial death rate of children in an endemic area, however, we have here the evidence supporting this first example of balanced polymorphism in man.

There may well be other advantages conferred by the hæmoglobinoses. It is noteworthy that some thalassæmics and some people whose hæmoglobin consists entirely of E or D have a blood picture resembling that of compensated iron deficiency. It is possible that such people can adapt themselves more easily than others to a diet deficient in iron or to loss of iron by chronic hæmorrhage due to hookworms. The most convincing evidence so far, however, relates to interaction with malaria.

Although not all populations living in malarious regions show an abnormality of hæmoglobin synthesis in some of their members, hæmoglobinoses have only been found at an appreciable frequency where malaria is also present. This is particularly notable in Africa where the Highlands of Kenya are free from sickling. Indeed, there have been attempts to deny an anthropological significance of the distribution of the hæmoglobinoses altogether, and to relate their presence or absence entirely to the selective advantage they confer or might confer on a malarious population. A glance at the map (fig. 7) will show that this is too extreme a view (*see also* Haldane, 1956). Nevertheless, it is remarkable that in contrast to many other primitive

aboriginal populations the Australians are free from hæmoglobinoses—malaria was not introduced into Australia until a few generations ago.

INCREASING IMPORTANCE OF THE HÆMOGLOBINOSES

Malnutrition and infectious diseases are on the decline in many countries where hæmoglobinoses are frequent. On the other hand, we know of no effective therapy and can use only palliative measures when we are confronted with a hæmoglobinopathy. It must be expected that the disorders of hæmoglobin synthesis will become increasingly important in many parts of the world. In the Lake Kopias area of Greece, where sickling and thalassæmia are frequent but where the once formidable malaria has now been eradicated, the hæmoglobinopathies are now the most pressing medical problem. It has been calculated that in the Commonwealth countries of West Africa alone three of every hundred children born should suffer from a hæmoglobinopathy. Whilst the over-all wastage of life before puberty was high this percentage was insignificant, but the higher the standard of public hygiene and the greater the improvements in nutrition the more significant will be this figure. In Italy marriage advice bureaus have been introduced in areas where thalassæmia is frequent. With an increasing standard of education and with a greater insight into the genetics of the hæmoglobinopathies similar services will be required in the African territories.

The hæmoglobinoses are also of medico-legal importance. I was present in Africa when two men claimed to be the father of the same child—a girl who would later bring in a valuable bride price. The problem was quickly settled by the pathologist when he found that the infant, but not her mother, was a sickler, and that of the two contestants only one was a sickler only. Hæmoglobin as well as the blood groups may be of more than theoretical interest when blood transfusions are given. Edington (1956) has described a post-mortem examination on an anæmic woman from the Gold Coast—a non-sickler—who had been transfused with two pints of AC and one of SC blood. The spleen was enlarged, grossly congested and in its histology not unlike the spleen seen in sickle-cell crisis. It was thought possible that the transfusion of the SC blood had been contributory to this woman's death.

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TONSILS AND ADENOIDS: EVALUATION OF REMOVAL IN 50 DOCTORS' CHILDREN

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It is practically impossible to absorb all that has been written about tonsils and adenoids and the results of their removal. It seems that an unusually accurate assessment, so far as children are concerned, might be made by studying the result of the operation upon doctors' own children, for there would be the great benefit of skilled observation of the illnesses for which the operation was undertaken and the results achieved. This analysis has been made upon 50 consecutive operations on doctors' children which I have performed in the last ten years or so, the parents having replied to a circular letter setting out the child's medical history before operation, asking for the effect on each symptom, for a general comment and ending with this sentence—'I know you will realize that I want a true report, even if it shows that the operation did not have all the good effects for which we hoped'. The series has the further advantages that the case histories and clinical examinations were made by one individual, who also performed all the operations according to a dissection technique evolved by three generations of surgeons at The Hospital for Sick Children, Great Ormond Street, where the indications for, and technique of, the operation have had serious and careful study for fifty years.

SCOPE OF INVESTIGATION

The indications for the operation were those accepted as a result of the accumulated experience of the medical and surgical staff of a large children's hospital, for the wise policy at that hospital has been that any member of the consultant medical or surgical staff may decide upon the operation; thus the specialist surgeon has a wide over-all knowledge of current opinion among pædiatricians, which is observed to change with changing years.

The case histories and doctor-parents' comments upon them and upon the results of the operation make up a large table, and since the object here is to present, in an easily assimilable form, an analysis of a highly selected small series, it seems best to discuss each symptom and its frequency and the result of the operation upon it in a separate paragraph. The paragraphs are arranged in order of frequency of symptoms, but it will be understood that many of the children had several of the symptoms and some of them all, and also that such a limited series does not display all the indications

for the operation. No mention is made of the size of the tonsils and adenoids, although size of adenoids is inferred in nasal obstruction relieved by their removal. This is because the decision for the operation is based chiefly upon a careful history, and only in a minor way upon the size and appearance of the tonsils and adenoids, with some rare and rather startling exceptions which would not happen in taking the history from a doctor-parent. Tonsils and adenoids of an individual child vary in size and appearance in a most remarkable way, so that a description of their physical characteristics is only of value if based on repeated observation. In 1909, George Waugh stated that it is the 'septicity' of the tonsils and not their size which matters.

There is no example in the series of recurrent mesenteric adenitis dependent upon swallowed infection from bad tonsils; no example of tuberculous cervical adenitis; no case of rheumatism or nephritis; no child with insomnia and night-terrors and bed-wetting. But all of these may be definite indications that the tonsils and adenoids should be removed. Nor is there an example of prolonged poor health due to toxic absorption from the tonsils and adenoids, without a diagnosis of the source of the trouble having been made. Such 'sub-clinical' chronic tonsil infection is not uncommon in children's practice, but a doctor-parent would have noticed repeated redness of the throat and persistent enlargement of the tonsillar cervical glands, and probably a slight rise of evening temperature when his child was particularly off colour. It is in such children that the result of removal of the tonsils and adenoids is so often followed by a dramatic improvement in general health and growth.

Years ago it was the size of the tonsils and adenoids which condemned them; more recently the tonsils have been regarded chiefly from the point of view of sepsis and as foci of infection, whereas the size of adenoids is still a major consideration. Now we try to balance up the harm they are doing against the good they may still do as defensive and immunizing centres, and we remember that in the best circumstances it is a very safe operation.

Only children who had their tonsils and adenoids removed are included in the series. Often adenoids alone are removed when the symptoms are mainly attributable to them; or because it is thought wiser, in the first few years of life, to give the tonsils the benefit of any doubt so that they may continue to exert their immunizing function; or in the hope that resumption of nose-breathing when the adenoid obstruction is relieved will give the tonsils an opportunity to recover their condition. This hope is often doomed to disappointment.

There is no rigid age barrier and no insurmountable difficulty in the operative technique in the young child; but it seems right to demand more severe indications, especially regarding the tonsils, in the first few years of life for they have had such a short time to exert their ordinary function and to establish that their disease is beyond reasonable hope of spontaneous recovery.

The youngest child was 2 years old and the oldest 15 years, the average age being five years and seven months. There were 30 boys and 20 girls, and the children were presented at a fairly even rate during the ten years. At the beginning of that period spring and summer were the times of election for the operation, but later on the control of common infections, particularly streptococcal, by chemotherapy or antibiotics robbed the winter of its chief drawback, and more recently the incidence of poliomyelitis in late summer has made the early spring the time of choice. It is also then that a succession of upper respiratory troubles stimulates the parents and doctors to take definite action to overcome them.

TONSILLITIS AND INFLAMED THROAT

Number of children 42. *Cured* 20. *Improved* 19. *No change* 3.

The most common complaint of the parents of the 50 children was of inflammation in the throat; half were called tonsillitis and half red throats with temperature. It is perhaps in the diagnosis of this that the greatest value was reaped from the parents being doctors, for it is well known that children seldom complain of a sore throat, and examination of the throat is often the only means of establishing the cause of a febrile illness. As might be expected the rate of cure of this condition was high, because how can a child with no tonsils get tonsillitis? It is often stated, however, that after tonsillectomy children continue to suffer from inflammation in the throat—pharyngitis instead of tonsillitis. This finds no support in this series because, apart from the 20 who had no more sore throats, 19 had fewer sore throats, mostly far fewer, and only three remained as susceptible to them as before operation.

OTITIS MEDIA AND DEAFNESS

Number of children 35. *Cured* 23. *Improved* 8. *No change* 3.
Onset after operation 1.

With these doctor-parents the occurrence of otitis media, amongst other troubles in the nose and throat, was often the factor which stimulated them to seek surgical advice. Their belief that ear infection often comes from infection in the tonsils and adenoids, chiefly the adenoids, is confirmed by the results of having them removed in their own children. Of 35 with otitis media 23 of the children had no more troubles, and only three were not improved. One child who had not had otitis media before operation has had several mild attacks during the four years which have elapsed since. Included in these numbers are three children who had had recurrent deafness without any pain or obvious inflammation in the ears; two of them had no more deafness, and one was said to be perhaps a little deaf still, but there had been no recent test.

CERVICAL GLAND ENLARGEMENT

Number of children 33. *Cured* 21. *Improved* 9. *No change* 3.

None of the patients was presented only because there were enlarged

cervical glands, but in a number of them such glands had rightly made the parents suspect infection in the lymphoid tissue in the nasopharynx. Enlargement of the tonsillar gland is a valuable sign of tonsil sepsis and it is remarkable how seldom other foci of infection in the mouth and throat affect this gland, except indirectly through the tonsil; indeed if it is found to remain enlarged after tonsillectomy experience leads one to suspect an infected tonsil remnant, or tuberculosis. Septic absorption from the naso-pharynx causes enlargement of a number of superficial glands in the posterior triangle of the neck, the most usual combination of causes being post-nasal discharge from naso-sinusitis in a child whose adenoids have not been removed, or who has adenoid remnants. Although there was no example of tuberculous glands in this series such a condition certainly demands the removal of the tonsils and adenoids since they are the portal of entry of the tubercle bacillus. Of the 33 children who had enlarged cervical glands, in only three was there no marked improvement following the operation; the comments of their doctor-parents being: 'still palpable'; 'variable with infection'; and 'a few small, shotty cervical glands still present'.

COLDS

Number of children 26. *Cured* 0. *Improved* 20. *No change* 5. *Worse* 1.

The separation of this complaint from the two subsequent ones of nasal obstruction and nasal discharge is difficult and perhaps arbitrary. None of the doctor-parents brought their children just because of ordinary colds, but because they had found the colds unusually frequent and severe, often with pyrexia and red throat, or because they were accompanied by persistent nasal obstruction and discharge. One has always felt that it was too much to expect of a surgical procedure that it could prevent colds, the actual cause of which, probably a virus infection, still eludes us, but for many years I have had the impression that a child subject to severe colds is benefited in this respect by the tonsil and adenoid operation. This impression dates back some fifteen years when my two daughters had their tonsils and adenoids removed. But the number of doctors in this series who had the same experience was satisfying: 20 out of 26 children who had suffered severely from colds were reported by their parents to be greatly improved, and in only five was there thought to be no change.

The explanation may be that during a cold the infection lurks about in the irregularities on the surface and in the crypts of the tonsils, which are highly absorbing structures with profuse lymphatic drainage which carries the virus toxins into the blood stream causing a febrile illness. The cold also causes swelling of the adenoids which then obstruct the nasal passages so that they are not readily cleared. Muco-pus lying in the nasal cavities keeps up the inflammation of the underlying mucosa and its weight and sticky consistency prevent the action of the cilia. There can be little doubt that a properly cleaned nose recovers from a cold much more quickly than a neglected one, or one in which the discharge is sniffed back into the

nasopharynx and on to the adenoids. Colds in babies are difficult to manage because the baby readily adopts mouth-breathing and cannot blow his nose. The toddler may instigate swelling and growth of his adenoids by sniffing infected discharge backwards. The well-brought-up child saves his adenoids by blowing his nose properly, and his tonsils by eschewing mouth-breathing, and the infant may be helped to overcome a cold by sucking the discharge out of the nose with an all-rubber rat-tailed syringe. But if there is a failure and the tonsils and adenoids enlarge and become infected their removal seems very beneficial to colds in respect of their frequency, severity and duration. The one child in the series who had more severe, but not more frequent, colds suffered a bad nasal and sinus infection a month after operation.

NASAL OBSTRUCTION

Number of children 22. *Cured* 11. *Improved* 11.

The majority of these children had colds accompanied by severe nasal obstruction and continued to have a blocked nose between colds. The result of the operation was that half of them were cured, and the other half improved only, perhaps because they had never completely overcome their mouth-breathing habits, and suffered from recurrent congestion of their nasal mucosa. More rigorous breathing exercises were probably indicated. Of seven children who had nasal obstruction without excessive colds, six were cured, and one was reported as only improved.

NASAL DISCHARGE

Number of children 19. *Cured* 9. *Improved* 9. *Worse* 1.

It has been mentioned in the paragraph about colds that excessive nasal discharge may occur during colds because the child is unable to clean his nose properly due to swelling of the adenoids. If the adenoids remain swollen between colds the nasal air-currents are not able to maintain that freedom which is essential for the health of the nasal mucosa and it becomes congested and catarrhal, continuing to secrete excess of mucus or mucopus. The child has persistent nasal discharge which can, judging from this series, be improved or cured by removal of the adenoids. There is one exception, the child who developed nasal sinusitis during convalescence.

CHEST INFECTIONS AND COUGH

Number of children 10. *Cured* 2. *Improved* 4. *No change* 4.

Not many of the children's parents complained of cough, and when they did it was attributable to two main regions: nasopharyngeal and chest. Nasopharyngeal barking cough may be due, amongst other reasons, to discharge from infected adenoids, or to mouth-breathing causing a dry throat, and less often to large tonsils. It is readily improved by removing the offending structures and by nose-breathing instruction. The other type of cough—of pulmonary origin—may be due to infection passing down

from the throat into the lungs or to cold air from mouth-breathing. In this series there is one child whose father is convinced that removal of the tonsils and adenoids was a major factor in preventing repeated attacks of bronchitis. Years ago one often heard it said that infection was more likely to pass to the lungs if it were not caught up in the tonsils. Such a belief seems to have died a natural death, and perhaps this series will serve as one more nail in the coffin since in no case were more coughs or chest infections attributed to the absence of the tonsils and adenoids.

ALLERGIC MANIFESTATIONS

Number of children 7. *No change* 6. *Improved* 1.

An allergic child's tonsils and adenoids should be removed only on their own demerits as sometimes infection in them may precipitate an allergic attack.

GENERAL HEALTH

Number of children 50. *Improved* 35.

The removal of tonsils and adenoids, if it improves or cures some of the illnesses which indicated the need for the operation, must have, to that extent, a good effect upon the general health of the child. Apart from that it has often been observed that there is an improvement in growth and well-being, which is sometimes most impressive. It seems that doctors as a whole are rather critical of the health and growth of their own children, but it is gratifying to find the parents of 35 out of these 50 children asserting that they have benefited generally, some very greatly.

SATISFACTION WITH THE OPERATION

Number of children 50. *Satisfaction* 40. *Partial satisfaction* 6. *No satisfaction* 3. *Adverse criticism* 1.

The question of being satisfied or not with the result of the operation was not put directly to the doctor-parents but they were asked for a general comment and from this it transpires that the parents of 40 were satisfied, those of six did not express themselves as feeling that the operation had achieved all they had hoped and three thought there was no benefit. One, a psychologist who described his child as an 'individualist', hopes that he may prevent permanent harm resulting from the child's separation from her parents; he was unfortunate not only because his child, of ten years, was very unhappy in hospital, but also in her being one of the three out of 35 children with otitis media who were not improved as a result of the operation.

GENERAL CONCLUSIONS

The removal of tonsils and adenoids is now under one of the clouds of disfavour which have obscured its merits for a few years at a time on several occasions during the present century. This seems particularly unwarranted at the present time when it is carried out with much more care and safety than in the past. If the operation is improperly performed and pieces of

tonsil and adenoid are left behind the patient is usually worse off than if nothing had been done, but such sad occurrences, although they happen, are much less frequent than they were. More painstaking care is still called for, particularly in the removal of adenoids (the most difficult part of the operation) because injury to the delicate muscles of the upper pharynx may lead to irreparable damage of the first sphincter of the respiratory-alimentary tract, and incomplete removal to worsening of the ear condition which possibly dictated the need for operation. Tonsil remnants are often more badly infected than the untouched tonsil, and cause more trouble.

The acute illnesses due to infection of the tonsils and adenoids—tonsillitis, peritonsillar abscess, otitis media and mastoiditis possibly leading to lateral sinus thrombosis and meningitis—can mostly be evaded by the prompt use of the chemotherapeutic drugs or antibiotics. This is a great advance which we all appreciate, and none more than those whose misfortune it was to deal with them. But it seems a little doubtful if all minor infections should be treated with these powerful drugs, and even more doubtful if it is wise to use them as maintenance drugs over long periods to 'maintain' freedom from infection. Do children now grow up without having had a good opportunity of developing natural immunity to common infections, so that they are often ailing rather than occasionally ill? No doubt tonsillitis was a sharp illness, if short; but children recovered from it before the modern drugs were discovered, and perhaps upper respiratory infections left the child with more immunity then than he now gets a chance to acquire. It is always possible to resort to antibiotics and chemotherapy if an infection threatens to get out of hand, and by a conservative use of such agents it may well be that fewer strains of resistant organisms will be bred.

The tonsils and probably the adenoids are a small part of the defensive and immunizing mechanism of the body. They suffer heavily in the fight against invading organisms. The object should be to remove them only when they are judged to be doing more harm than good, when the illnesses dependent upon them outweigh the probable ability of the damaged organs to continue efficiently their proper role of defence. The results of the operation depend upon the proper selection of the cases and the proper execution of the operation. The children in this series were carefully considered by their parents and the surgeon, and the results seem to have justified the means.

The emphasis laid on infection and function must not cause us to ignore the mechanical troubles which may result from the large size of tonsils and adenoids which is the deciding factor against them in a minority of cases. Nor must the over-simplification of a short survey blind us to other causes of some of the symptoms which have been discussed. It was hardly possible, and perhaps unfairly misleading, to avoid reference to nasal sinusitis when discussing colds, nasal obstruction, nasal discharge and cough.

POLIOMYELITIS AND THE OPERATION

It would be inopportune to refrain from mentioning poliomyelitis when writing about the tonsil and adenoid operation. If a patient is infected with the poliomyelitis virus it tends to settle in those motor neurons which are in a poor state, whether due to fatigue or to a local injury in that particular part of the body which they serve. Hence great general fatigue is said to predispose to widespread paralysis, and local trauma may determine paralysis of the muscles in the injured region of the body. The nerves which supply the region of the tonsils and adenoids are the 9th and 10th cranial nerves, springing from the medulla oblongata, and so the trauma of the tonsil and adenoid operation may lead to that form of poliomyelitis which causes paralysis of the vital centres in the bulb. The same danger lies in any operation in the region of the naso- and oro-pharynx. Public attention, however, has been focused on the tonsil and adenoid operation because fatalities due to bulbar paralysis have occurred and been noted following it, but only because it is much the most frequent operation carried out in this region. It is obviously unwise to carry out any operation on the mouth or throat in a district where the incidence of poliomyelitis is high, because the chances that the patient has already been infected with poliomyelitis, or will become so before the wound is completely healed, are greater then. An immunizing injection against poliomyelitis should not be given within six weeks before or after a tonsil operation.

SUMMARY

Advantages are claimed for studying the results of the tonsil and adenoid operation upon a small series of doctors' children rather than upon a larger unselected series where observations would not be so accurate.

A high proportion of cures and improvement is shown for the well-recognized complaints which called for the operation: tonsillitis, sore throats, otitis media and deafness, cervical gland enlargement and severe colds. It was particularly gratifying to find so many children having fewer and less troublesome colds following the operation. There was an improvement in the general health of the majority of the children and the doctor-parents of 40 of the 50 children were well satisfied with the result of the operation upon their own children; six were not so certain of great benefit, and four seemed to think it had not been worth while.

Modern opinion upon the indications for operation is considered, emphasis being laid on the much greater value of the history of illness than on the examination of the tonsils and adenoids.

There must be convincing evidence that they are doing more harm than good before their removal is advised.

The relationship between poliomyelitis and the tonsil and adenoid operation is explained.

ACUTE EPIGLOTTITIS
SUPRAGLOTTITIS

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THERE is no more alarming experience for a conscientious general practitioner than to be confronted, after an urgent call, with a dead or dying child whom he has seen some hours previously and diagnosed as suffering from a simple infection. The best example of such an occurrence is the Waterhouse-Friderichsen syndrome (meningococcal septicæmia). This is an uncommon but regular annual entry among the causes of unexpected sudden death discovered by those who carry out medico-legal necropsies for the Coroner. Most general practitioners can recollect in their practice an instance of a young child dying unexpectedly in these tragic circumstances. To this must now be added acute laryngeal obstruction from acute epiglottitis (supraglottitis) due to *Hæmophilus influenzæ* (type B).

FIG. 1.—Example of brawny œdema of the epiglottis in a typical fatal case.

EARLY CASES

It was in 1950 that at necropsy one of us (F.E.C.) saw an appearance of the epiglottis which seemed to be so localized as to suggest some specific disease. This lesion consisted of a brawny œdema of the epiglottis (fig. 1) causing acute laryngeal obstruction. No other organic changes were noted on naked-eye or on histological examination, but the histological appearance of the epiglottis was one of an acute inflammatory reaction with a cellular infiltration which appeared at the time to be by round cells but were, in fact, immature polymorphonuclear cells. Surface bacteriology showed no organism which could be really incriminated. The history was one which has since proved to be typical of the disease:—

A male child, aged 5 years, was perfectly healthy at 8 a.m. While having breakfast he complained of 'pain in the throat and back of the neck'. The family doctor was called and found a temperature of 103° F. (39.4° C.) but no physical signs. The pharynx appeared to be normal. During that day the doctor called again at least three times and although the child persistently refused solid food, he still could find no obvious physical signs. At 11.30 a.m. the child had a sudden convulsion and died.

In February 1950 the following two cases came under the care of one of us (H.M.J.) within a few days of one another.

A female child of 1 year 8 months was admitted to hospital with extreme stridor and died within a few minutes of admission. The previous day she had suffered from a slight cold and soreness in the throat. Two hours before admission she had suddenly had a choking fit and stridor and was rushed to hospital by her parents.

A female child, aged 2 years, was admitted with severe stridor which had been present for six hours before admission. She breathed with difficulty and there was expiratory stridor accompanied by severe intercostal recession. X-ray examination of the chest was clear. Laryngoscopy showed gross œdema and redness of the epiglottis and arytenoid cartilages. The white cell count was 16,000 per c.mm., with an excess of lymphocytes. An intratracheal tube was left *in situ*, antidiphtheritic serum was administered with penicillin, 100,000 units three-hourly, and chlortetracycline, 0.125 g. six-hourly. She collapsed and died 48 hours after admission. A culture swab taken direct from the larynx showed hæmolytic streptococci.

Both these cases were reported to the Coroner and a necropsy was carried out by one of us (F.E.C.). Both showed a very swollen epiglottis and supraglottic œdema above the vocal cords. There were no other obvious changes in any of the other organs.

In the light of this experience, the cases were discussed by us in some detail. It was determined that if a further case presented itself, in addition to medical treatment early tracheotomy would be far better than intubation and would mechanically by-pass the obstruction in the larynx. It was more than six months before such a case was admitted to the Ear, Nose and Throat department of the hospital. In the meantime further cases were seen in the course of routine post-mortem examinations and eventually *H. influenzæ* (type B) was isolated from culture of the epiglottis in two cases.

REVIEW OF LITERATURE

A search of the literature showed that before the 1918 pandemic of influenza, laryngeal diphtheria was thought to be the only cause of acute infectious 'croup' causing acute laryngeal obstruction. In the 1918 epidemic, however, it was recognized that there were other non-diphtheritic infections causing acute œdema of the larynx, glottis and subglottic regions. To this condition the term acute laryngo-tracheo-bronchitis was applied. More recently it was noted that among these cases were some in which the acute inflammation and œdema were localized to the supraglottic, arytenoid and epiglottic regions, resulting in acute laryngeal obstruction. A case of septicæmia with acute laryngitis due to *H. influenzæ* was described by de Nevasquez (1942), but apart from that the condition had not been recorded in England. On the other hand, in the United States reports had been published of epiglottitis due to *H. influenzæ* (type B). In 1941, Sinclair reported ten cases; in 1942, Alexander ten more; in 1943, Du Bois and Aldrich reported four; Stephen

reported one in 1946 and finally Davis three in 1947. The fullest description is that of Miller (1946) who analysed the admissions into the Los Angeles Children's Hospital during 1946, when there were eight cases.

Rabe (1948) revived the term acute infectious croup and analysed 347 cases admitted to hospital between 1937 and 1946. He divided them into three categories: (a) Diphtheritic. (b) *H. influenzæ* (type B). (c) 'Virus' croup. Twenty-eight fell into the second category.

In December 1950, a further case was seen (H.M.J.):—

This was in a boy aged 5½ years. Sixteen hours before admission he complained of soreness in the throat, cough and hoarseness. This was followed two hours before admission by stridor and difficulty in breathing. An x-ray of the neck and chest was taken to exclude a possible foreign body: the films were clear. Laryngoscopy showed a brawny red swollen epiglottis. A bronchoscope was passed, blood-stained mucus aspirated from the trachea, and tracheotomy was performed. Following on operation chlortetracycline was given by mouth; steam inhalations were used to moisten the air and after a stormy first two days he made a good and uneventful recovery. A swab taken from the larynx in this case grew *H. influenzæ* (type B) sensitive to chlortetracycline and slightly sensitive to penicillin.

In 1953, Camps reported a series of 19 cases seen at necropsy between 1944 and 1952, from two of which *H. influenzæ* had been isolated by deep culture. Comparisons of age and seasonal incidence suggested that they were the same condition as that described by the various American authors. Since then five more cases have been seen, from all of which *H. influenzæ* (type B) has been recovered and in one case only a purulent meningitis due to the same organism was demonstrated—a more advanced stage of that described previously (Camps, 1953).

TWO CASE RECORDS

Interest in the subject of epiglottitis was reawakened when the following two cases, which were successfully treated, were encountered by H.M.J.

A male child, aged 2 years 1 month, was admitted to hospital on December 3, 1955. Eight hours before, on the morning of admission, the child had been off colour and would not eat. At 5 p.m. on the same day he suddenly developed great difficulty in breathing and this gradually got worse. By 11 p.m. the same evening, when first seen by the surgeon, the child had a grey pallor, extreme stridor, and recession of the lower ribs and supraclavicular areas. Breath sounds over the whole chest were absent. Laryngoscopy showed a red, swollen epiglottis. Immediate tracheotomy under general anæsthesia was carried out. Chlortetracycline was given: 0.125 g. four times a day—intravenously on the first day, and then by mouth on the following and subsequent days. The child made an uninterrupted recovery and the tracheotomy tube was removed on the tenth day.

A female child, aged 3 years 5 months, was admitted *in extremis* on December 23, 1955. The history, as given by her own private doctor, was as follows: 'This little child was first seen by my deputy on the evening before her admission to hospital. He found her coughing a little and complaining of some shortness of breath. He was not worried about her condition and prescribed an antispasmodic cough mixture. I saw her next morning and she seemed quite comfortable, her throat was then a little injected and her chest revealed an odd rhonchus. There was slight pyrexia: 100° F. (37.8° C.). I was next called to see her at about 8 p.m. on the night of her admission and was greeted on arrival with a child desperately ill: she was cyanosed and gasping for breath but with scarcely any air entry sounds to be heard. Her throat looked rather red and swollen. In view of the extreme urgency of the case, I took the child along to hospital myself in my car'.

Examination at the hospital showed a child almost moribund, with great difficulty in breathing. Laryngoscopy showed an œdematous red epiglottis. Immediate, unsterile, urgent tracheotomy was carried out, with improvement in the child's condition. Chlortetracycline, 0.125 g., was given four times daily: intravenously on the first day and then by mouth. The child made a good recovery and the tracheotomy tube was removed on the tenth day.

It is as a result of these successes that it is felt that the attention of general practitioners and pædiatricians should be drawn to the existence of the condition, how to diagnose it and the treatment to be instituted in order to save the patient's life.

ETIOLOGY AND PATHOLOGY

Acute epiglottitis may be defined as 'An acute inflammatory œdema of the epiglottis causing laryngeal obstruction due to swelling and immobilization of the structure'.

In our series of 29 cases there was a slight predominance of males (17 males and 12 females). More than half the children (15) were between the ages of two and five years. Four were under one year of age, five were aged 1 to 2 years, four were aged 5 to 6 years, and only one (aged 12 years) was over the age of 6 years. There was a marked preponderance of cases (25) in the winter (October to March).

The specific infecting organism is *Hæmophilus influenzæ* (type B). In most of the cases, the lesion has been limited to the epiglottis. Histologically there is a diffuse infiltration with immature polymorphs with some inflammatory œdema. On account of the anatomical structure of the epiglottis, that part of the structure which has the mucosa closely applied to the cartilage shows less swelling. On occasion the organism has been demonstrated in sections and all recent cases (i.e. since 1951) have yielded pure cultures of *H. influenzæ* (type B) on deep culture (introduction of saline into the submucosal tissue after searing). There appears to be no extension upwards into the lingual lymphoid tissue or to the pharynx, nor is there any extension down into the subglottic region: in other words, it is a pure supraglottic lesion. Severe ulceration of the mucosa has not been seen, but careful examination has shown slight surface ulceration in one or two cases. In none of the cases has any remote lesion been demonstrated other than meningitis (two cases); in both of these the initial diagnosis was *Hæmophilus influenzæ* meningitis and purulent fluid had been withdrawn on lumbar puncture.

In the first case the naked-eye appearance of the epiglottis appeared to be within normal limits but sections showed round-celled infiltration whilst in the second case the child died suddenly with laryngeal obstruction and the epiglottic lesion (naked eye) was typical.

Toxic changes have not been obvious but in spite of this, after initial relief of the obstruction, immediate recovery has not taken place although there is much improvement. The child has remained ill for anything up to forty-eight hours. It is clear that there has been a septicæmia; the American workers have obtained positive blood cultures.

CLINICAL PICTURE

The history, several typical examples of which have already been quoted, is characteristic. The early symptoms are insignificant, slight soreness in the throat, poor appetite and slight cough being the only complaints. Clinical examination of the chest reveals no significant changes. Pyrexia is often high. These are followed a few hours later by the sudden onset of acute upper respiratory obstruction and stridor, accompanied by shock and severe prostration, and a rapidly progressive course of the disease, The reason for the apparent suddenness in the onset of these dangerous symptoms is that the laryngo-pharynx is a relatively large space into which the swollen tissues can expand and it can accommodate extreme swelling of the structures without much difficulty. Because of this, the doctor is led to believe that he is dealing with a mild case of 'croup'. Here lies the danger, for with lightning-like suddenness the patient's condition can be gravely altered. A slight increase in the already extreme œdema, a fit of coughing, or movement may displace the swollen and loose supraglottic structures. They may be drawn into the glottis, between the vocal cords and quickly plug the lumen. There is a sudden sense of choking and the patient responds with frantic inspiratory efforts which make matters worse and jam the swollen tissues down ever more tightly. The patient is often asphyxiated before help can be given.

In those cases reaching hospital, there is stridor, both inspiratory and expiratory, with intercostal retraction and retraction of the supraclavicular areas. Examination of the chest reveals absence of breath sounds.

The sudden onset of these severe symptoms, accompanied by a complaint that the throat hurts on swallowing, is typical and it has often been suspected that the child has inhaled a foreign body, a sweet or a bone. When time was available, this possibility was excluded by an x-ray of the chest and soft tissues of the neck.

DIAGNOSIS

This depends in the first place upon recognizing that the condition exists and suspecting it in all young children suddenly taken ill. The rather sudden onset of upper respiratory obstruction, usually with high fever and slight or absent premonitory symptoms, is characteristic. Symptoms of shock or prostration are out of proportion to the short duration of the respiratory difficulty.

The appearance of the epiglottis confirms the diagnosis. Firm pressure with a spatula at the base of the tongue will sometimes reveal the swollen epiglottis. This was found to be difficult and in the cases quoted which came to operation a laryngoscope was gently inserted and found to be necessary to get a good view of the epiglottis and larynx. Nastruck (personal communication), however, does not approve of the use of the laryngoscope as he has seen sudden collapse after its use but states that the epiglottis can be seen by drawing the tongue forward. No harm, however, appears to have been done in our cases by laryngoscopy.

Examination of the chest by careful auscultation is of value: the absence of breath sounds indicates obstruction high up in the respiratory tract suggesting acute supraglottitis. The presence of crepitations is good evidence that obstruction is not the major factor because a fairly large volume of air is

	Laryngeal diphtheria	Laryngotracheitis	*H. influenzæ* (type B) epiglottitis
Onset and course	Insidious: 2 to 4 days	1 to 2 days	Sudden: 6 to 12 hours
Hoarseness	+	+	— (or muffled)
Fever	Low	High	High
Difficulty in swallowing	—	—	+
Dyspnœa	Slow course	Faster	Fastest
General appearance	Moderately ill, flushed	More ill, flushed, feverish. Inspiratory and expiratory. Dry. 'Crowing'.	Extremely sick. Prostrated. Pale. Inspiratory mainly. Gulping and gasping. Tongue may protrude.
Oral examination	Membrane usually over tonsils and pharynx	Pharyngeal mucosa inflamed. Glottis inflamed. Marked swelling of subglottic tissues.	Pharynx slightly injected. Swollen, fiery red epiglottis. Swelling usually limited to epiglottis.
Smear and culture	*C. diphtheriæ*	Streptococci most frequent	*H. influenzæ* (type B) by quellung reaction

TABLE I.—Differential diagnosis of acute epiglottitis.

required to expand the moist alveoli. A high leucocyte count is usual in epiglottitis. The whole course of the disease is a matter of hours.

The *differential diagnosis* lies primarily from laryngeal diphtheria and acute laryngotracheitis (table I).

TREATMENT

Early recognition followed by immediate admission to hospital is most important.

Relief of respiratory obstruction.—The treatment *par excellence* is tracheotomy. It by-passes the obstruction, facilitates the removal of thick tracheal secretion and does not press on swollen inflamed tissues. It is safest to perform this at once. As already shown, in young children waiting is extremely dangerous. Tracheotomy is imperative if there is:—

(a) Restlessness. This is an important index of the severity of the obstruction; a restless child is an air-hungry one.

(b) Cyanosis.

(c) Deep retraction of the intercostal spaces and supraclavicular region.

(d) Absent breath sounds.

Antibiotics.—Chlortetracycline is the drug of choice. In the first successful

case we met, *H. influenzæ* was isolated and found to be highly sensitive to this drug, and only moderately sensitive to penicillin. In our two most recent cases it was given intravenously, 0.125 g., in the first instance and repeated by intravenous injection if the condition warranted it and if there was difficulty in swallowing fluids. It was continued for a week in these two cases, by which time full recovery was assured.

Helium oxygen was administered in one case and the child nursed in an oxygen tent. No other antibiotics were used and none was found to be necessary.

Removal of tracheotomy tube.—The tube is left in for ten days, then plugged for a short while. If there is no distress or cyanosis, it is removed. In the most recent cases, the tube was removed on the 10th day without ill-effect. A dry dressing is applied to the wound, which quickly heals.

Intubation was tried in one of our patients who died, and was found to be most unsatisfactory. It is not advised because it causes pressure on the swollen inflamed tissues and the latter become irritated by the tube. Further, should it get blocked by secretion, it is much more difficult to clear than a tracheotomy tube.

CONCLUSIONS

Acute epiglottitis appears to be a definite clinical entity which has been, and still can be, easily confused with acute laryngo-tracheo-bronchitis. As, however, the course is quite different and requires acute emergency measures, it is essential that it should be recognized early and this is primarily the task of the general practitioner. The fact that 26 out of 29 cases have come to Coroner's post-mortem examinations is a challenge to the general practitioner, the pædiatrician and the laryngologist.

A combination of early recognition, admission to hospital, tracheotomy, and chlortetracycline intravenously and by mouth, has led to successful treatment in three cases. We believe that there are probably very mild examples of the condition which are unrecognized and which recover spontaneously, possibly due to the empirical use of antibiotics.

All hospitals which admit small children should have an emergency tracheotomy set ready at all times, so that acute emergencies due to laryngeal obstruction can be dealt with immediately. Now that laryngeal diphtheria is so very uncommon there is a tendency to relax one's vigilance. Not only should the tracheotomy set be available but its whereabouts known to all the operating theatre staff.

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THE TREATMENT OF HÆMORRHOIDS

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'And telling me the sovereign'st thing on earth was parmaceti for an inward bruise'.
—*Henry IV, Part I*

THIS titbit of medical news voiced by a 'popinjay' at the end of a hard-fought battle infuriated the exhausted Harry Hotspur much in the same way as today the same remark might move a medical practitioner to derisive comment. It is not clear from the context whether the 'inward bruise' referred to was a bruise earned in the battle since it was an irrelevant remark. Might it not have had some other meaning? If a pile be an inward bruise, then there is historical precedent going back three hundred-and-sixty years for the treatment described here.

Parmaceti, the modern name for which is spermaceti, is a wax derived from the head of the sperm whale. Its main ingredient is cetyl palmitate or cetaceum. This is the active principle in 'parmacetyl' tablets, which also include small amounts of ethyl hydroxyethyl cellulose and magnesium hydroxide, to combat the constipation so often associated with piles.

At first sight, the oral route seems an unnecessarily long approach to a pile, but it has obvious æsthetic and hygienic advantages, and it avoids the pain of inserting a suppository against an inflamed pile. The active principle in oral treatment must not be absorbed to any great extent in its passage through the bowel if it is to reach the rectum in adequate concentration to be effective. McIsaac (personal communication) has studied the behaviour of waxes in the bowel and reports that not more than 25 per cent. of cetaceum is absorbed in transit and that at least 70 per cent. arrives in the rectum unchanged.

SCOPE OF INVESTIGATION

To exclude the possibility that any beneficial effects of treatment were due to the small amounts of aperients in the tablets, cachets containing equivalent weights of pure cetaceum were made up and their effects compared with those of the tablets. Batches of ten consecutive patients were given either tablets or cachets. Twenty-five patients received tablets and twenty-five had cachets.

Treatment consisted of taking tablets or cachets morning and evening: three for the first two doses and thereafter two at a time until a total of ten or twelve had been taken. If a first course was not effective within a week, a second similar course was given. Alcohol and aperients were forbidden. The tablets were too large to swallow whole with comfort and were therefore crushed in a spoon and then swallowed with a full glass of water.

Abdominal, rectal and proctoscopic examination was carried out at the

first visit and again after one week and at any subsequent visit, unless pain or anal spasm made it impracticable. In such cases proctoscopy was postponed until a later visit, when it could be performed without distress. Symptoms complained of included pain, pain on defæcation, irritation, bleeding, discharge and prolapse. Cases were classified according to the state of prolapse: 1st degree where there was no prolapse; 2nd degree where prolapse occurred only after defæcation and spontaneously reduced; 3rd degree where the piles remained prolapsed.

RESULTS

The results are summarized in table I. Subjective relief was a marked feature but a successful result was not claimed unless it could be seen that there was also objective improvement. Bleeding had to stop and the inflammation to subside. It was not required that prolapse should be improved.

	Successes		Failures		No. of cases	
	'Parmacetyl'	Cetaceum	'Parmacetyl'	Cetaceum	'Parmacetyl'	Cetaceum
1st degree	12	11	3	1	15	12
2nd degree	4	2	1	0	5	2
3rd degree	3	5	2	6	5	11
Total	19	18	6	7	25	25

TABLE I.—Comparison of results obtained with 'parmacetyl' tablets and cachets of cetaceum in treatment of hæmorrhoids.

The results obtained with the tablets and the cachets were equally effective. No side-effects were experienced by any of the patients.

1st degree piles.—Fourteen of the 23 successfully treated patients in this group responded by the end of the first course. The other nine required two courses. They included two with granular proctitis and one with inflammation and ulceration of the sigmoid colon. This patient was given propantheline as well as 'parmacetyl' and both colon and piles cleared up in a fortnight. Three cases showed a delayed response; that is, they resolved after a period of about two weeks after the end of treatment. There were four failures, all due to the persistence of constipation.

2nd degree piles.—Four of these seven patients were relieved at the end of one course. One relapsed a month later, but responded to another course in a week. Another patient had a granular proctitis which required two courses before it subsided.

3rd degree piles.—In this group symptomatic relief was more marked than objective improvement. Bleeding stopped easily enough but the prolapsed piles tended to remain inflamed. Nevertheless, in eight out of the 16 patients, the condition completely subsided and in three the piles were reduced to 2nd degree prolapse. One patient relapsed after three weeks and again after three months, responding each time to further courses of treatment. One relapsed after four months, but responded to another course.

DISCUSSION

Before treating a patient with piles it is important to establish the cause, particularly excluding carcinoma of the rectum. Careful history-taking with particular reference to change in bowel habit, weight loss and dyspepsia is important. Physical examination or instrumentation should reveal any mass in the rectum. Proctoscopy is important in order to assess the state of the piles which are not palpable unless thrombosed.

Medical treatment cannot cure a prolapsed pile. All third-degree and most second-degree piles require surgery. Some first-degree piles have reached such a condition that surgery offers the best hope of a permanent cure. Constipation must be corrected or medical treatment is doomed to failure. The aim, then, of medical treatment is to give subjective relief, to stop bleeding and to cause inflammation to subside. Within these limits cetaceum proved a successful form of therapy. There was little to choose between the tablets and the cachets, but the tablets were easy to take and had the added advantage of containing a small dose of aperient.

'Parmacetyl' tablets are effective in most cases of 'acute piles'. Nearly all first-degree piles will respond to them. Bleeding in second- and third-degree piles is soon controlled. Inflammation in these degrees is more difficult to bring under control but there is quite remarkable subjective relief. They are valuable in the preoperative treatment of piles in that there is considerable reduction in the inflammation, if not complete resolution. The presence of granular proctitis does not make the prognosis worse as it responds readily to this form of treatment. The response is in fact so good that it suggests that 'parmacetyl' by mouth might be effective in conditions in the colon such as ulcerative colitis but this has not yet been investigated.

SUMMARY

A new form of treatment for piles, oral 'parmacetyl' tablets, was investigated. A similar number of cases was treated with oral cachets of cetaceum, the wax used in 'parmacetyl'. Fifty cases were treated in all.

Both forms of treatment were equally successful, confirming that it was the wax which was effective: 23 out of 27 cases of 1st-degree piles settled down; six 2nd-degree and eight out of 16 3rd-degree cases responded satisfactorily.

It is not suggested that this treatment can replace surgical therapy, but it is a valuable preoperative measure.

Its best use is for attacks of 'acute piles' and for 'bleeding piles', but the remarkable subjective improvement noticed after its use makes it valuable even in chronic cases.

No side-effects were experienced.

I wish to thank the many general practitioners of North Kensington and Hammersmith who helped by sending me cases; Mr. L. A. Ives, surgeon at this hospital, for his observations on the cases upon which he operated; and Dr. R. Mackarness and the E.G.H. Laboratories who provided the tablets and cachets.

CONFUSING THE ISSUE

PSYCHOSES AS SYMPTOMS OF CANCER

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Amid the flood of 'senile and demented' elderly patients, who today occupy about a quarter of the total hospital beds in the country, there is a definite percentage whose mental symptoms cloak bodily disease and confuse the issue until a post-mortem examination establishes the diagnosis. A recent series of necropsies has shown a group of patients with cancer whose obvious mental symptoms had only made confusion worse confounded. Their histories illustrate some of the peculiar problems which distinguish geriatrics from the ordinary run of general medicine.

CASE RECORDS

M.J.B. was admitted to St. John's Hospital, Battersea, as an alleged senile dement. She was filthy, neglected, wasted and pale. Extensor plantar responses and absent tendon reflexes raised the possibility of pernicious anæmia with subacute combined degeneration of the spinal cord. Death took place on the third day after admission and necropsy was performed. This revealed an ulcerating carcinoma of the stomach with secondaries in liver, spleen and lung. Some cerebral softening was also present.

E.E.F. came into hospital on account of mental confusion. She became comatose and died without presenting any definite physical signs. At post-mortem examination we found a carcinoma of the rectum, with secondaries in the liver. The brain appeared normal.

S.M.F. presented headache, restlessness and delusions. His necropsy diagnosis proved to be carcinoma of the prostate, with secondaries in liver and aortic glands.

F.M., admitted as 'senile, confused, incontinent', was found to have a carcinoma of the ovary, invading the other abdominal organs.

M.B., labelled 'senile dementia', showed delusions and would not let anyone look after her. Apart from some bronchitis, the only physical sign was a small nodule in one breast. At necropsy this proved to be malignant, with secondary deposits in pleura and lungs. The brain showed some wasting and atheroma of vessels.

M.A.E. was also admitted as 'senile dementia'. She died two days later. A large malignant ulcer of the stomach was found at necropsy, in addition to diverticulitis with peritonitis and marked calcification of aorta, mitral and aortic valves.

DISCUSSION

All these patients were aged between 80 and 90 years. In every one of them the mental symptoms completely overshadowed the physical signs. Most of them were non-cooperative and difficult to examine. None of them was suitable for careful pathological investigation or x-rays. In many instances the symptoms were of recent origin, so that the cases appeared to be senile psychoses. It is therefore important to realize that in old age a new growth can have mental confusion as its chief presenting symptom.

GENERAL PRACTITIONERS' FORUM

THE HOME NURSING SERVICE

A PLEA FOR 'DISTRICT ASSISTANT NURSES'

By R. L. KITCHING, M.B., B.S.
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THE general public are beginning to realize how much suffering there is that could be relieved by a better home nursing service, but there is little evidence that the authorities have any idea of the extent and urgency of the problem or how to solve it. This is borne out by the Report of the geriatrics joint subcommittee of the British Medical Association (1955). There are 92 paragraphs and 21 recommendations and the home nursing service is disposed of in one paragraph of 12 lines (compared with 24 lines required by chiropody). The shortage of nurses is dealt with very quickly and easily:

> '. . . establishments should be reviewed in the light of the needs of the elderly sick and infirm. It is recommended that a greater number of male nurses should be recruited to these services. In addition, a proportion of both male and female State-enrolled Assistant Nurses should be employed for duties within their scope. . . .'

INSUFFICIENT DISTRICT NURSES

The shortage of district nurses is an extremely serious matter and it is getting worse; it will certainly be many long years before there are enough district nurses so the sooner the question of assistants is re-examined the better. The solution of the problem lies in two facts: much of the district nurses' work could be done by less well-trained assistants, and there is a good deal of nursing that the district nurses cannot do which the assistants could do very well and which would be of the greatest comfort to the patients. For example, a district nurse cannot sleep in a patient's house and she cannot take duty as a night-nurse, but an assistant could sit up at night and would be a great comfort to the patient and a great help to the relatives and the doctor. There is much she could do with very little training; there are all sorts of small services and kindnesses for which patients are often inexpressibly grateful and which are true nursing. There are so many new therapies these days that the curative value of kindness is apt to be overlooked in the training schools. Another example of work which a district nurse cannot undertake is to be at a patient's house at a given time each day, although this sometimes makes a great difference to the patient's welfare, as in the case of old people who are getting helpless and soon become bed-fast if they are not washed and dressed punctually each day.

There is one service that an assistant nurse could render which is exceptionally important because it is one which the district nurse has to refuse.

Owing to the shortage of nurses all the district nurses are now midwives and are therefore not allowed to prepare the dead for burial. This is a serious matter because in these days there are no other trained women to do it and relatives are often extremely distressed about it. Trained assistant nurses would be able to render a valuable service in this way.

NURSES AND FAMILY PRACTICE

The prevention of suffering is not the only reason for getting assistants for the district nurses as soon as possible. A second reason is that it is important to get back to the old-fashioned family practice before it is completely destroyed. The whole Welfare State depends ultimately upon the quality of the family doctors and it is not realized by the authorities that it is quite impossible to get good family doctors without good family practice. For that there are three main requirements and we have only got two of them. We have the houses we want, with every conceivable facility for treating patients at home; and we can get a consultant out whenever we want one. The third essential is a nurse and in the old days we could always get one. She was usually an untrained amateur but she was often a very good nurse, and she made it possible to treat the patient at home. But nowadays there are so few nurses that nearly all our interesting cases have to be sent to hospital and therefore we cannot get any good family practice. And, of course, if more patients could be treated at home there would be other great benefits: it would set free hospital beds that are urgently needed; and it would be the greatest comfort to patients who dread being sent away, especially to those who ask for nothing but to be allowed to die at home—the last freedom. And surely a natural, inalienable right.

The first step towards a solution of the problem is to appreciate how big it is and how dreadful it is. The present neglect of the aged sick is as disgraceful as the callous disregard for the safety of children on the roads. Miss E. A. B. Davis reported on her examination of the home nursing problem in February 1955. She envisaged a service of state-trained nurses helped by voluntary workers, bath attendants, night attendants, sitters-in and so forth. A mixed team of this sort is probably the best that can be done to meet the acute emergency, but it would never do as a permanent home nursing service.

IMPORTANCE OF QUALIFIED NURSES

In a permanent service there must be a rigid rule that if a district nurse wants help in *nursing* the patient the helper must be a nurse; if she wants help in the house she can get a Home Help who is an extremely valuable member of the Public Health Department but is not a nurse. There must be the same distinction between nurses and other helpers as there is between doctors and other helpers. A nurse is a woman who has certain qualities and is trained; the training is a matter of discipline, knowledge and skill; the skill is acquired by constantly practising the techniques she was taught

in hospital. Nurses must be qualified and registered by a controlling authority. It is extremely important that the local government authorities should take every care to avoid any action that might seem to countenance unqualified nurses. The Civil Defence authorities seem to need watching on this point. Nurses must be qualified but that is not to say that there can be only one qualification.

The fact that there is a shortage of full-time nurses does not mean that there must necessarily be a shortage of part-time nurses. There are at present many women who want to earn a pound or two a week by part-time work and a few preliminary inquiries indicate that enough of them could be recruited to help in the home nursing service if they were appealed to in the right way and if the working conditions were made attractive. Of course, if there were enough State-enrolled assistant nurses (S.E.A.N.) they would solve the problem at once but there are none to be had and it takes about two years to train them.

DISTRICT ASSISTANT NURSES

It would be for the General Nursing Council to decide whether it would be better to shorten the training of the S.E.A.N. or to establish a new service of part-time 'district assistant nurses' with a much shorter training. Forty years ago it took four years to train a nurse and seven years to train a soldier, but it was found in both world wars that efficient soldiers could be trained in about nine months. No doubt nurses could be trained as quickly in war time but it would be difficult to get the necessary discipline in peace time. Discipline could not be enforced without some system of punishments and that seems hardly practicable at present, quite apart from other considerations. Self-discipline can be learnt reasonably quickly if it seems worth while, but on a national scale in peace time it would require a long process of education. It seems certain therefore that the shortage of nurses will not be made good in our time unless it is treated as a national emergency—unless, in fact, women are conscripted.

It will be said, of course, that one volunteer is worth three conscripts. The reply to this is twofold. In the first place, experience in two world wars proved that it is not true; and secondly, we cannot go on any longer waiting for volunteers while old people are suffering as they have not suffered for a hundred years.

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CURRENT THERAPEUTICS

CX.—THE USE OF BEMEGRIDE IN BARBITURATE COMA

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THE discovery that nalorphine (*N*-allylnormorphine) has a specific and selective antagonism to the respiratory depressant actions of morphine has provided an effective means of reversing the most dangerous effects of acute poisoning with morphine and similarly acting substances, such as methadone. The mode of action of nalorphine in reversing morphine-produced respiratory depression must remain a matter of conjecture until more is known of the action of morphine on the central nervous system, but the chemical structure of nalorphine and morphine is so similar that it must be considered possible that the receptors in the central nervous system which are affected by morphine can be blocked by nalorphine. This pharmacological relationship between the two drugs would be similar to that which exists between acetylcholine and atropine. It is not surprising that nalorphine is ineffective in counteracting the respiratory depressant effects of barbiturates since the action of barbiturates on the central nervous system is different from that of morphine.

Whilst acute morphine poisoning is now rather rare, the frequency of barbiturate poisoning is a problem of growing importance, and attention has been drawn to the increasing number of deaths from this cause (*Lancet*, 1951). As this death rate only reflects the much larger incidence of acute barbiturate poisoning which does not end fatally, and which has resulted from the extensive prescription of this group of sedatives and hypnotics, the therapy of barbiturate poisoning is now a problem of much greater magnitude than that of morphine poisoning.

Before discussing bemegride, the recently introduced analeptic, the treatment of barbiturate poisoning in general will be discussed.

THE TREATMENT OF BARBITURATE POISONING

The treatment of barbiturate-induced coma is a matter which has aroused some controversy, and in the past the issue has been clouded by the fact that danger to life in any case depends, broadly speaking, not only upon the amount of barbiturate consumed and absorbed, but to a large extent upon the nature of the barbiturate. The outlook in poisoning from a drug of short or medium duration of action is invariably better than that from poisoning by a long-acting member of the group. The features of barbiturate coma which combine to lead to a fatal outcome are: (1) Anoxæmia primarily due to respiratory depression but aggravated by obstruction of

the respiratory passages by mucus and collapsed soft tissues which results from the loss of laryngeal and pharyngeal reflexes. (2) Hypotension produced by central depression and possibly by certain effects on the peripheral autonomic nervous system. (3) Infection of areas of pulmonary atelectasis leading to fatal broncho-pneumonia. If this cycle of events can be broken by proper management so that anoxæmia and hypotension are prevented and renal function maintained, there is no theoretical or practical reason why even the most severe barbiturate coma should not recover, as in time the drug will be detoxicated or excreted, and recovery from coma will coincide with a decline in the amount of barbiturate in the blood (Wright, 1955).

It has become clear that analeptic drugs play a role of secondary importance in the treatment of barbiturate poisoning as compared with that of general measures designed to relieve or prevent anoxæmia. Treatment should be started as early as possible and requires skilled and constant supervision. This means that admission to hospital is necessary.

At the outset of treatment *gastric lavage* may remove a significant amount of unabsorbed barbiturate and should be performed in every case. A large-bore stomach tube should be used and, to avoid undue risk of aspiration of fluid into the lungs, lavage should be carried out with small volumes of fluid by means of an apparatus such as Senoran's evacuator. An adequate airway must be achieved by the aspiration of mucus and fluid from the tracheo-bronchial tree and soft-tissue obstruction be prevented by passage of an endotracheal tube if necessary.

Oxygen should be administered by a mask, nasal catheter or other method dictated by the state of the patient. The position of the patient is of importance and he should be nursed in a lateral decubitus position. The head-down posture is best avoided. In severe cases, in which tidal exchange is much reduced, respirations slow and cyanosis marked, complete apnœa may occur and respiration may have to be maintained by the use of an effective mechanical respirator. It is in the prevention of this complication that the new drug, bemegride, finds its greatest use.

When hypotension is marked, the blood pressure may be raised by the administration of plasma or a suitable plasma substitute. *Adequate fluid intake* should be ensured by the intravenous infusion of 2 litres of 5 per cent. glucose over twenty-four hours. Excessive intravenous fluid administration may lead to pulmonary œdema and cannot be justified on the grounds that it will accelerate the excretion of barbiturate, as the long-acting barbiturates are but slowly excreted by the kidney and the rate of excretion is not significantly increased by increasing urinary output. Throughout treatment the urinary output must be carefully observed and this is most effectively achieved by regular catheterization. The amount of urine secreted must be taken into account in determining the volume of fluid administered parenterally.

The risk of pulmonary infection is reduced by the prophylactic adminis-

tration of an antibiotic such as *penicillin*, and care should be taken to avoid damage to the eyes during the handling of the unconscious patient.

There is general agreement on the value of the type of treatment outlined above but considerably less accord regarding the use of analeptics such as nikethamide, picrotoxin and amphetamine. Whilst these drugs have many protagonists, there is little convincing evidence of their effectiveness (Report to Council on Pharmacy and Chemistry, 1936, 1939; Eckenhoff and Dam, 1956).

The main danger associated with the use of analeptics is the risk of inducing convulsions with subsequent severe medullary depression. Cardiac arrhythmia may be induced and vomiting may occur with aspiration of vomited material. In anoxia surprisingly small doses of analeptics such as nikethamide may occasionally induce convulsions. The advantage to be expected from the use of analeptics is an increase in tidal volume and elevation of blood pressure. That these effects can be elicited is undoubted but they are short lived, and frequent injections must be given. In the case of picrotoxin, a considerable latent period elapses between the time of injection and the onset of its stimulant effect so that the result is somewhat unpredictable, and dangerous convulsions may be produced.

THE CHEMISTRY OF BEMEGRIDE

Bemegride ('megimide') was first synthesized in 1911 and was investigated by Shaw *et al.* (1954) as a barbiturate antagonist. It was found by animal experiment and clinical trial to be an effective analeptic in barbiturate poisoning, showing a much longer duration of action than analeptics hitherto employed. Bemegride is a white crystalline substance sparingly soluble in water with the following structural formula (fig. 1):—

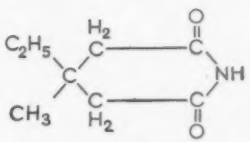

FIG. 1

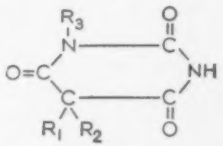

FIG. 2

FIG. 1.—Structural formula of bemegride.
FIG. 2.—Basic structure of the barbiturates. R_1, R_2, R_3 are radicals varying in different barbiturates.

This structure bears certain obvious similarities to the basic structure of the barbiturates (fig. 2).

THE PHARMACOLOGY OF BEMEGRIDE

In animal experiments it is found that bemegride antagonizes the hypnotic and respiratory depressant action of barbiturates in rabbits, dogs, rats and mice, with rather less dramatic effects in the cat. Given to an animal which has previously received an anæsthetic dose of a short-acting barbiturate,

bemegride causes an increase in respiratory rate and tidal volume associated with a return of reflexes and an arousal to consciousness; subsequently the animal may sleep but can be aroused by handling. Given to an animal not

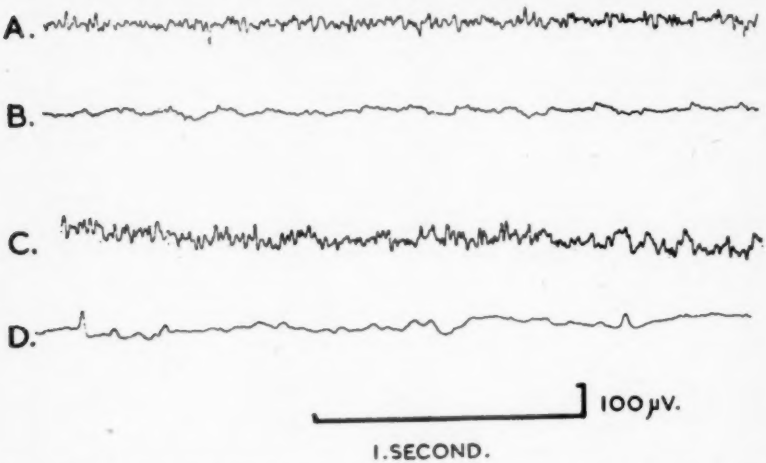

FIG. 3.—Electroencephalograms showing the effect of bemegride in a rabbit anæsthetized with pentobarbitone. (A) Awake. (B) Pentobarbitone, 40 mg./kg. (C) 5 minutes after B. Bemegride 20 mg./kg. (D) Control. 5 minutes after B. No bemegride given (Cass, 1956).

under the influence of a barbiturate, a relatively small dose of bemegride will cause convulsions which can be stopped immediately by an intravenous administration of a barbiturate. If an animal is rendered comatose by the use of a long-acting barbiturate, bemegride will cause a significant increase in the rate and depth of respiration with restoration of reflexes and spontaneous movement. The duration of intensity of this effect depends upon the dose. Large doses of bemegride may induce such a high degree of hyper-excitability that in response to handling the animal may be thrown into convulsions. These effects in animals are similar to the effects in man.

It has also been shown (Cass, 1956) that bemegride restores the normal electroencephalographic pattern in rabbits when the electroencephalogram has been depressed by a barbiturate (fig. 3). On the other hand, the pattern of deep depression produced by other non-barbiturate sedatives and hypnotics is not affected by bemegride. A similar reversal of the electroencephalographic pattern of barbiturate depression in man by bemegride has been demonstrated by Louw and Sonne (1956). These observations suggest that bemegride may have a specific action in antagonizing the depressant effects of barbiturates on the central nervous system rather than a non-specific central stimulant action. Final conclusions on this latter question must, of course, await much fuller pharmacological investigation, both of the action of barbiturates on the central nervous system and of

bemegride, but the striking effects seen in animal experiments suggested the use of the drug in barbiturate coma in man. A striking and interesting feature of the action of this drug is that, by comparison with other analeptics such as nikethamide, the duration of stimulation of respiratory centre is much longer and the degree of response more easily controlled by varying the dose.

CLINICAL USE OF BEMEGRIDE

In 1955, Shulman *et al.* (1955) reported the effects of bemegride in barbiturate poisoning in man and recommended that, in addition to the usual general method of dealing with the comatose patient, treatment with bemegride should be supplemented by the use of amiphenazole ('daptazole') (2:4:diamino-5-phenylthiazole). The routine treatment recommended by these authors consists of slow intravenous infusion of 5 per cent. glucose, so that 10 ml. of 0.5 per cent. solution of bemegride (50 mg.) can be injected into the tubing leading to the intravenous cannula. This injection is repeated according to the needs of the patient every three to five minutes, each injection being preceded by 1 ml. of a 1.5 per cent. solution of amiphenazole. Amiphenazole is an analeptic which causes arousal in morphine narcosis and also shows to some extent an analeptic action in barbiturate coma, but subsequent experience with this form of treatment favours the conclusion that of the two drugs bemegride is by far the more active, and it is doubtful if amiphenazole contributes significantly to the efficiency of treatment. Clemmensen (1956) suggests that the bemegride should be given by continuous intravenous drip of 100 ml. of saline containing 500 mg. of bemegride over a period of thirty minutes, the injection being interrupted after 300 mg. have been given.

Following an injection of 50 mg. of bemegride in barbiturate coma in man, there is evidence of central stimulation. There is a marked increase in the rate and depth of respiration, an increase in the pulse rate and a rise in blood pressure, the colour of the skin and mucous membranes improves, and there may be evidence of arousal in that the patient responds to painful stimuli and deep superficial reflexes return. Swallowing and coughing may occur and tone returns to flaccid muscles.

The striking difference between the action of bemegride and analeptics such as nikethamide is seen in the duration of action of the former. The action of nikethamide is momentary, lasting two to three minutes, whereas the duration of action of bemegride is much more prolonged and the effect of a single injection may last for fifteen to twenty minutes or longer. The effect of a single 50-mg. dose of bemegride depends, however, upon the depth of central depression which in part at least depends upon the amount of the barbiturate in the blood, and it is necessary to repeat the injection of bemegride at intervals dictated by the response of the patient, the objective being to maintain the patient in a state of light coma. As might be expected, the dose required for this is smallest and the response most

dramatic in patients poisoned with a short-acting barbiturate. In many of these cases a central nervous system stimulant is scarcely necessary but, at the other end of the scale, in patients who have been poisoned by a long-acting barbiturate, and have been profoundly comatose for some time, frequent injections must be given, and if anoxæmia and hypotension have been severe and prolonged before the beginning of treatment, neither bemegride nor any other drug may be of any avail.

Because of the wide variation in the severity of barbiturate poisoning and of the influence on prognosis of factors such as the type and quantity of barbiturate ingested, the degree of absorption of the ingested drug, the time which has elapsed between the onset of the coma and the institution of treatment, the possible existence of previous addiction, and the fact, often unknown to the physician, that other central nervous system depressants have been taken, it is difficult to plan a suitably standardized clinical experiment to discover the value of a given form of treatment in barbiturate coma. A recommended treatment therefore tends to be favoured or neglected on the basis of impressions gained from relatively limited experience. There is, however, an increasing literature of published and well-documented evidence tending to show that in severe barbiturate coma bemegride is of undoubted value as a respiratory stimulant to counteract profound respiratory depression (Kjaer-Larsen, 1956) and that the beneficial effects are of much longer duration than those of nikethamide and other analeptics. At the same time, it is becoming apparent that significant as these effects are bemegride has little effect on the duration of unconsciousness; this is determined by the amount of barbiturate in the blood and is not influenced by bemegride, as there is no chemical interaction between the two drugs, nor does bemegride affect the rate of elimination of barbiturate.

SIDE-EFFECTS OF BEMEGRIDE

Convulsions.—In common with other analeptics bemegride may cause convulsions if given in excessive quantity. The convulsive state can be terminated by raising the blood barbiturate level by the injection of a small quantity of a short-acting barbiturate. This complication is seen more often in poisoning with short-acting barbiturates than in that which follows long-acting drugs. Shaw *et al.* (1954) recommend that during treatment with bemegride thiopentone should be readily available to meet this emergency. By proper care in the administration of bemegride, however, and careful observation of the response of the drug, convulsions during treatment should not occur. It is well recognized that generalized epileptiform convulsions may occur in barbiturate addicts when the barbiturate is rapidly withdrawn. This suggests the possibility that bemegride may cause convulsions by displacing barbiturate from specifically sensitive receptors in the central nervous system, an unlikely explanation, since addicts and non-addicts appear to be equally liable to this complication. Further, it has already been noted that other short-acting analeptics in excessive dose may

cause convulsions in barbiturate coma.

Vomiting.—If the dose of bemegride used is excessive, reflex activity may be enhanced to a degree sufficient to induce vomiting. This event in the unconscious patient is undesirable, as it may lead to the aspiration of gastric contents with consequent pulmonary complications. Vomiting during bemegride administration can be readily avoided by careful observation so that respiration is maintained without excessive reflex activity.

Psychosis.—Kjaer-Larsen (1956) has reported the occurrence of a delayed delirious psychosis in 15 patients out of a series of 50 cases of barbiturate coma treated with bemegride. The psychosis developed between the 1st and 4th day after recovery from coma, and mental disturbance was of a fairly uniform pattern characterized by visual hallucinations of colours and shapes, auditory hallucinations which often relate exactly to events in the patient's past, loss of orientation in time and space, and delusions which have a definite relation to previous experience. This psychotic state leads to considerable confusion and inattention and may last for as long as seven days. It is not exclusively seen in barbiturate addicts and is more likely to occur when large doses of bemegride have been used.

CONCLUSIONS

In the treatment of barbiturate coma general management directed to the relief of anoxia, the maintenance of blood pressure and the prevention of pulmonary infection take precedence over other forms of treatment.

Experience in the past two years has shown that bemegride is of undoubted value in the treatment of severe barbiturate coma with profound respiratory depression or apnœa.

Its main value lies in its analeptic and respiratory stimulant effects which, with care in administration, can be maintained over long periods without ill-effects.

Another possible use of bemegride, which has not yet been fully investigated, is its use in terminating anæsthesia from short-acting barbiturates, when the patient's cooperation is desirable and a rapid return to consciousness is required.

I am indebted to the Editors of the *British Journal of Anæsthesia* for permission to reproduce fig. 3.

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EQUIPPING THE SURGERY

II.—DRESSINGS AND ANTISEPTICS

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In contrast to surgical instruments, which are equipment, dressings and antiseptics are expendable stores. The doctor can get those that he wants for any particular purpose from the chemist, and he requires to keep in his surgery only those most likely to be needed in an emergency.

DRESSINGS

The general purpose of a dressing is to protect a wound, or to apply medicament to an open or a healing surface. The dressing appropriate to any lesion will depend upon its size, its site, and its nature.

First-aid dressings.—The name is used for a small dressing applied immediately to a minor breach of surface, a cut, prick, blister or small burn, or to the sutured incision of a small operation. First-aid dressings are supplied under that name by leading manufacturers, usually in boxes of assorted sizes.

DRESSINGS FOR LARGER LESIONS

A dressing must protect a wound from mechanical injury and from bacterial contamination. At the same time it must allow evaporation from the skin, and absorb any discharge, so that the surface is kept as dry as possible. Maceration of the skin by sweat or pus favours the multiplication of bacteria and prevents healing, whilst unabsorbed discharge becomes an albuminous track, leading from the surface of the dressing to the wound, that encourages the entry and growth of contaminant bacteria.

The dressing must be retained in contact with the lesion but yet allow movement of that part.

The standard dressing materials today are absorbent gauze, cotton-wool, and open weave bandages; all three are made from cotton fibre.

Surgical gauze is woven in a loose mesh. It is supplied in rolls, nine inches (23 cm.) wide, of eight ply or layers, but it is made up in the hospital, or supplied by the manufacturers, in squares or oblongs of various sizes and ply, either folded so that the cut edges are inturned, or stitched at the sides.

Cotton-wool is supplied in sheets, that are moderately compressed and put up in rolls which may be interleaved with paper. It is sold by weight and comes in various qualities. The best quality—B.P.C.—is the most absorbent, and should be used for dressings. The cheaper, so-called hospital, qualities serve for padding, and for an outer layer over better quality wool.

Bandages.—The most useful are the ordinary rolled white, open-wove,

B.P.C. type, 3, 4, or 6 yards long (2.75, 3.5 or 5.5 metres), and 1, 2½, or 4 inches (2.5, 6.5, or 10 cm.) wide. Two other types are useful.

'*Kling*' bandages are of cotton, loosely woven with the individual fibres taking an undulating course. They are useful to secure dressings over parts of irregular contour such as the neck or the joints where the warmth, pressure, or cost of crêpe bandages is not desired.

Crêpe bandages are woven of crimped material that usually contains some wool. They have an elasticity that allows them to lie smoothly over a curved surface and to exert a steady pressure.

Adhesive plaster and bandage.—Where a dressing is to be kept in position for some time, some form of adhesive plaster or bandage is usually preferred. The adhesive substance, which has a rubber basis, is applied to a specially woven cloth which may be rigid or provide a certain amount of elasticity. The most useful type for fixing dressings is made with minute gaps or perforations in the adhesive layer, so that evaporation can take place through the plaster. Some patients are sensitive to rubber adhesive. For them plaster with a different basis can be obtained.

STERILITY OF DRESSINGS

Many dressings are sold as sterilized, but that means no more than that they have been through a sterilizing process. Nothing remains sterile unless it has been transferred directly from the sterilizer to a sealed packet impervious to air or moisture. Dressings that have been sterilized and kept in clean and dust-free surroundings, however, are unlikely to become contaminated with pathogenic organisms.

Manufacturers put up sterile packets of swabs, of gauze pads, of wool or of the dressing materials required for a minor operation or a single dressing. The practitioner will require a few of these for primary dressings. For most purposes portions cut from bulk materials with sterile instruments and handled under aseptic conditions can be used.

DRESSINGS FOR OPEN WOUNDS

The features of an open wound are that its base is covered with granulations and its edges are fringed with thin growing epithelium, both of which are easily damaged. Its surface discharges pus or serum which must be absorbed by the outer layers of the dressing.

Some non-stick material must be laid on the surface, but none of these is entirely satisfactory; either they stick a bit, or they are waterproof and cause maceration. The best substance is probably a fine gauze net impregnated with petroleum jelly: a preparation usually known as '*tulle gras*'. On this is laid gauze, plain or soaked in some medicament, which can be changed without removing the 'tulle gras' or injuring the granulations.

When the discharge is copious, the dressing must be covered with enough absorbent material to soak up the discharge and allow none of it to reach the outside surface. Best quality and sterilized wool need be used only for the

first layer. Afterwards cheaper wool, or cellulose tissue, which is cheap and highly absorbent, may be used.

FILM DRESSINGS

Quick-drying solutions, that leave a film of plastic material on the skin, have a limited use for dressing small wounds that are clean and dry. Such a preparation is 'nobecutane', which is supplied in tins with a spray nozzle. The advantages of such a dressing are that it is quickly applied, thin, barely visible, and comfortable. The disadvantage is that it is waterproof, and if applied to any but a small area it causes maceration.

ANTISEPTICS

Antiseptics are reagents that are lethal to bacteria, but harmful to a much lesser extent to human beings. In lesser concentration they can restrain the growth of bacteria without killing them. There are many types of antiseptics, acting in different ways, and suitable for different purposes. About the worst is Lister's original antiseptic, carbolic acid. The action of an antiseptic *in vitro* varies with concentration, with time and with temperature, and when used in the tissues its value is largely governed by its toxicity and its reaction with organic matter in the wound. The leading properties of the main varieties are as follows:—

(1) *Oxidizing agents.*—Nascent oxygen combines with any organic matter, and is not selective for bacteria. The chief value of hydrogen peroxide lies in the mechanical cleansing of a sloughing wound.

(2) *Halogens.*—Chlorine and iodine are rapidly bactericidal in extreme dilution. Their disadvantage is that they combine with any organic matter and that they are occasionally irritating to tissue.

Chlorine is usually employed as a solution of hypochlorite (eusol, Dakin's solution). Chlorine is also added to coal-tar derivatives such as 'dettol'. Iodine is usually used as a $2\frac{1}{2}$ per cent. solution in spirit. It is the best antiseptic for sterilizing the skin. Iodoform (CHI_3) has a wonderful 'antiseptic smell', but is entirely useless.

(3) *Heavy metals* (*mercury*, *copper*, *silver*, *zinc*).—These have little use in surgery, owing to their toxicity and their vivid colouring. Mercuric skin sterilizers, 'metaphen', thiomersal ('merthiolate'), and mercurochrome, owe their appeal to their attractive colour rather than their bactericidal efficiency.

(4) *Alcohols.*—The only one in common use, ethyl alcohol, owes its popularity largely to its universal availability, its cleansing powers, and its ability to dissolve many other substances such as iodine. It coagulates proteins, and is therefore ineffective in a wound, in spite of its use for that purpose by the Good Samaritan. It is chiefly used to sterilize the skin, and glass and steel instruments. The optimum bactericidal concentration is 70 per cent.

(5) *Coal tar derivatives.*—Of these, phenol is almost useless. The cresols are used, usually with soap, for large-scale disinfection of bedding and furniture. Tar acids are sold as proprietary disinfectants ('izal', 'cyllin') for

floors, drains and lavatories. Other antiseptics ('dettol') are cresols or xylenols with a chlorine atom added. The members of this group act fairly rapidly, they are non-toxic, they do not coagulate proteins and act in the presence of serum or blood, and their efficiency is increased by soap.

(6) *Aniline dyes.*—Most aniline dyes are bactericidal in high dilutions, and their action is interfered with only moderately by blood and serum. Their bright colour and staining properties limit their use in practice. Bonney's blue (brilliant green and crystal violet) is favoured for sterilizing the vagina. Gentian violet is the best antiseptic for staphylococcal infections of the face severe enough to justify temporary social ostracism.

(7) *Acridine dyes.*—The members of this group (acriflavine, euflavine, proflavine, 'rivanol') have been popular since the 1914-18 War. They disinfect in dilutions of 0.2 per cent. and are bacteriostatic in dilutions up to 0.0001 per cent. They are, for practical purposes, non-toxic to the tissues, and their activity is hardly interfered with by the presence of blood or serum. They are particularly active against *Streptococcus pyogenes.*

(8) *The newer antiseptics.*—*Cetrimide* (*'cetavlon'*) is a derivative of ammonium bromide, and is a detergent, much favoured for cleansing and sterilizing the skin. It is effective against streptococci and staphylococci, and relatively non-toxic.

Chlorhexidine (*'hibitane'*) is a new antiseptic, the chemical formula of which is bis-*p*-chlorophenyl diguanidohexane. It can kill streptococci *in vitro* in a dilution of 1/10.000,000. It has been favourably reported on in gynæcological practice by Calman and Murray (*Brit. med. J.*, 1956, **ii**, 200).

SUGGESTED EQUIPMENT FOR THE SURGERY

As pointed out earlier, anything that may be needed in the way of dressings and antiseptics can usually be obtained at short notice from the chemist, and the doctor need keep no more that a skeleton equipment in his surgery. The following are suggested as meeting ordinary requirements.

(1) *First-aid dressings*

A 'factory outfit' of mixed sizes.

(2) *Sterile dressings*

(a) A few packets of gauze pads, 4 x 4 inches (10 x 10 cm.) sterilized and in a sealed envelope.

A few 'multiple pack dressings' for first-aid, containing gauze, wool and bandages. These are put up by the manufacturing firms for use in the first-aid department of factories, according to the specification contained in the Drug Tariff issued by the Ministry of Health.

(b) *Ex-Army stores*

First Field Dressing (small).

Shell dressing (large). If obtainable from a disposal unit, these are useful for any kind of dressing. They contain a pad of wool covered with gauze, and a bandage in an impervious cotton

envelope. They were sterile when issued and can be sterilized again.

(3) *Stock dressings*

Gauze.—Packets of absorbent gauze, 3 yards by 36 inches (2.75 x 0.9 metre).

Wool.—First quality absorbent wool
Second quality wool
Cellulose tissue.
} These are sold by weight.

Bandages.—*Open weave cotton*, 6 yards (5.5 metres) by 1 inch (2.5 cm.), 2½ inches (6.3 cm.) and 4 inches (10 cm.).
'Kling' bandages, 6 yards (5.5 metres) by 4 inches (10 cm.) and 6 inches (15.25 cm.).
Crêpe bandages, 6 yards (5.5 metres) by 2½ inches (6.3 cm.) and 4 inches (10 cm.).

(4) '*Tulle gras*'—one tin.

(5) '*Nobecutane*'—one spray tin.

(6) *Antiseptics*

(a) Surgical or methylated spirit—1 quart (1 litre).
(b) Tincture of iodine.
(c) 'Dettol'.
(d) Tablets of acriflavine, for preparing 1/1000 solution.
(e) Chlorhexidine, 1/200 solution in 70 per cent. spirit, for keeping knives, scissors and needles.

Hydrogen peroxide and eusol, for dressing septic wounds, will be ordered as required.

REVISION CORNER

SNUFFLES

THE term 'snuffles', like some other conditions, such as 'wind', is more often used by mothers and midwives than by doctors. Surprisingly, most modern textbooks of pædiatrics make no mention of it except to state that snuffles is commonly a manifestation of congenital syphilis—a rare disease to-day.

ETIOLOGY

Snuffles is the audible effect of air passing through nasal passages partially obstructed by the secretion of mucus, which causes a bubbling sound. In mild degree this is quite common, and usually starts in the first week or two of life: sometimes the mother states that her infant was 'born with a cold'. The intensity and duration of the condition are variable, but in most cases a short mild course is seen. Occasionally snuffles may persist for a

year or more. There is no seasonal variation and no sex preference. The question whether the nasal obstruction is due to infection or to the secretion of excess mucus due to some other cause such as irritation, is not easy to answer.

The usual benign course, sometimes rather prolonged, and without any effect on the general health, suggests that the majority of instances are primarily non-infective, although secondary infection may occur at any time, and some babies clearly suffer from purulent rhinitis from the onset. These latter often have a clear history of contact with an adult in the household suffering from a respiratory infection. It would be better to regard such children as examples of infection who should be investigated and treated accordingly, and to reserve the term snuffles for the former group, in whom possibly some simple mechanical action, such as a sudden change of temperature, may cause a reaction in the nasal mucosa leading to an excess of mucus production, sufficient to cause symptoms only in small nasal passages. There is no evidence that allergy plays any part in the snuffles of infancy. In this connexion it should be noted that the infant's nose is more turned up than that of older people, so that foreign particles may enter more readily. Also, as the entrance is narrow, crusts may easily form and block the airway. Added to this, the choanæ, which cut off the nasal passages from the pharynx, are very small. The narrower nasal airway in premature infants doubtless accounts for the frequent occurrence of snuffles in these babies. For the same reason, a high incidence is seen in mongolism.

The nasal obstruction consequent to the condition has undesirable effects. The infant has great difficulty in breathing through the mouth, particularly for the first two to three weeks of life, as the tongue seems to act as a one-way valve which prevents air from passing from the mouth into the glottis. The greater the degree of nasal obstruction, the more likely is feeding difficulty to arise. This leads to refusal of food, choking and sometimes regurgitation with the risk of inhalation of vomit.

An infant with excessive nasal secretion rarely has much nasal discharge. The fact that the child spends most of his time recumbent means that secretions pass backwards into the nasopharynx, and may partly account for the alleged rarity of colds in small babies. In the usual case such discharge as there is is watery, but it may be too thick to appear.

Once established, snuffles leads to mouth-breathing which may be persistent. As a result the physiological functions of the nose are unused and the unmoistened, unfiltered air may set up pharyngeal irritation with subsequent infection and hypertrophy of the pharyngeal lymphoid tissue. Perhaps the development of 'adenoids' in infants may be assisted in this way and there is always the risk of nasal deformity developing in a long-standing case of nasal blockage.

Whether these children are more prone to pulmonary infection is uncertain—probably not, unless secondary nasal infection has taken place.

Conjunctivitis, in the form of the familiar 'sticky eye', is quite a common accompaniment.

DIAGNOSIS

This is usually simple, but *foreign bodies*, usually in the form of strands of cotton-wool, should be looked for. *Congenital choanal atresia* is exceedingly rare and affected infants appear very ill from anoxia if the atresia is bilateral. The successful passage of a rubber catheter through the nose into the nasopharynx will exclude this abnormality.

Œsophageal atresia with tracheo-œsophageal fistula, in which the œsophagus distal to the atresia communicates with the trachea, should be detected soon after birth. This is important, as the first feed will cause choking and vomiting with probable inhalation of the vomit. The abnormality should be suspected by the presence of *froth round the nostrils and mouth*. Oral secretions cannot be swallowed, so, mixed with air, they appear at nose and mouth, producing this characteristic sign in addition to snuffles. Failure to pass a catheter into the stomach will confirm the diagnosis.

Syphilitic snuffles is extremely rare nowadays. It does not generally appear until about the third week of life, and the discharge is profuse, purulent and blood-stained. Other signs of congenital syphilis will be present.

Cleft palate is commonly associated with snuffles and when, rarely, this is associated with maldevelopment of the mandible (Robin's syndrome), the condition is particularly troublesome. In this syndrome the poorly supported tongue tends to fall back and block the glottis.

Laryngeal stridor should be differentiated easily by the typical crowing sound on inspiration. The cause of this is an abnormally soft and folded 'infantile' larynx and the stridor generally disappears by the second year. Sometimes snuffles and congenital laryngeal stridor coexist in the same patient.

TREATMENT

When there is definite purulent discharge, a nasal swab should be taken to determine the causative organism and its sensitivity to the various antibiotics. In the usual, non-purulent case, the nasal airway should be kept clear, to avoid the evils of mouth-breathing. Cleansing the nose with cotton-wool is of doubtful value and may be dangerous, so when obstruction is marked, nasal drops may be tried. These should always be made up in isotonic solutions. Oily preparations should never be used owing to the risk of the development of lipoid pneumonia. Ephedrine, 0.5 per cent. in normal saline, may be tried; a drop in each nostril, three to four times daily, for a few days at a time. Perhaps the most important point of all is to try to establish nasal breathing in the more protracted cases by showing

the mother how to occlude the mouth manually for gradually increasing periods.

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BALDNESS

Alopecia in its different forms is not a simple problem, for the etiology ranges from hair-pulling to endogenous toxic agents, and hair growth is influenced by genetic, nutritional, endocrine and nervous factors. Diagnostically, it must be decided first whether there is accompanying atrophy or scarring. Thus alopecias can be classified broadly into cicatricial and non-cicatricial groups.

CICATRICIAL ALOPECIAS

Circumscribed baldness may result from a wound, burn or caustic agent, or from local disease of sufficient depth to involve the hair follicles. The scalp is left smooth, shiny, waxy or wrinkled, and the follicular orifices have disappeared. Cicatricial alopecia follows destructive processes such as rodent ulcer, lupus vulgaris, tertiary syphilides, or severe sepsis of the pilosebaceous apparatus, such as carbuncle, and pitted scars remain after varicella, variola and zoster. In general, folliculitis and other coccal infections leave characteristic round bald spots on which the hair eventually regrows, although sometimes only after some months. Likewise, except for favus and suppurative ringworm (*kerion celsi*), tinea capitis does not produce lasting baldness, although in the past the treatment sometimes did, and damage by x-ray epilation resulted in many cases of cicatricial alopecia. Nowadays, however, in expert hands and with accurate means of measuring x-ray dosage such a risk is practically non-existent.

The scalp may be the site of various chronic skin diseases which end in atrophy, such as scleroderma, lupus erythematosus and lichen plano-pilaris, and there is a supposedly 'essential' cicatricial disease of the scalp known as *pseudopelade* of Brocq, which is characterized by smooth, waxy, bald areas tending to coalesce in an irregular pattern and studded with occasional clumps of hairs. This, however, is now regarded as a doubtful entity.

Once the hair follicles have been destroyed for any reason the baldness is permanent and no treatment is of any avail.

NON-CICATRICIAL ALOPECIAS

The health of a patient is often reflected in the condition of his hair and a chronic general disease may cause a progressive alopecia. The function of the hair-follicles, however, can be inhibited suddenly, as may the growth of the nails, by a severe constitutional upset or acute infective illness (*symptomatic alopecia*). Thus, diffuse hair-fall, occasionally universal, may be a sequel to childbirth, operations, typhoid fever, erysipelas, influenza (as in the 1918 pandemic) and so on. When this happens it is almost

invariably nine weeks after, and the hair comes out with alarming rapidity. Complete regrowth, however, is the rule, no special treatment is necessary and the patient can be reassured. The alopecia of secondary syphilis, occurring from three to fifteen months after infection, is of similar toxic origin but has a more insidious onset, the distribution is patchy and the denuded areas (unlike alopecia areata) are not completely bald but have a 'moth-eaten' look. The hair recovers in due course.

'Idiopathic' *premature alopecia*, which, like senile alopecia, is far more common in men than women, usually begins before the twenty-fifth year with a slow symmetrical recession at the temples and progresses inexorably, leaving in some the effect of the tonsure and in others a vestigial tuft in front, the hair at the back and sides remaining relatively thick. A hereditary predisposition is traceable in many cases but this must be combined with androgenic stimulation and the etiology is far from clear. Pityriasis capitis has been traditionally blamed for premature baldness (*alopecia pityroides*) but the relationship is difficult to assess. Dandruff, however, if present, requires persistent local treatment; for instance, with sulphur and salicylic acid preparations or selenium sulphide shampoo.

Marginal partial alopecia in women affecting just within the fronto-lateral hair-line is generally due to repeated traction on the hair-roots by metal haircurlers and grips, combined often with over-zealous scalp massage and brushing in an upward and backward direction with a stiff hairbrush. Constant traumatization of this kind seems to cause lasting damage to the hair-follicles resulting in a failure of the hair to regrow even when the procedures are stopped. In over-anxious women, usually of middle age, who are worried or have feelings of insecurity, there is a tendency to become obsessional about their hair, imagining it to be coming out 'in handfuls', and it is sometimes difficult to convince them that they are not about to go bald at any moment.

Children are not infrequently found to have linear, ragged or bizarre-shaped bald areas, possibly suggestive of alopecia areata or ringworm, which are simply due to hair-pulling, either through nervous habit or by another child in play. In *trichotillomania*, a form of neurotic *tic*, there is an uncontrollable impulse to pull the hair out.

ALOPECIA AREATA

Circumscribed alopecia without atrophy generally means alopecia areata. The patches are sharply annular, completely bald and often have short hairs in the periphery which are darker and thicker at their distal ends, resembling 'exclamation marks'. These are of diagnostic value but also indicate that the function of the hair follicles is still deranged and that further extension is likely.

Alopecia areata in children is sometimes mistaken for non-inflammatory ringworm, but ringworm patches are covered with fine scales and stumps of greyish broken hairs. The diagnosis can be established quickly by

examining the scalp under Wood's light in a dark room, when the infected hairs in common ringworm show a green fluorescence.

The mechanism of alopecia areata is unknown. There is a familial tendency in some cases and in many a relationship with emotional disturbance, the commonest precipitating cause (about 25 per cent. of patients) being mental shock or acute anxiety. Often the regrowing hair is unpigmented, suggesting a connexion with *vitiligo*, and the two disorders are sometimes combined.

It is doubtful whether treatment makes any difference: e.g. high frequency, 'vibro-massage', ultra-violet light and other procedures beloved of 'scalp experts', but the patient must be told that spontaneous recovery occurs in more than 99 per cent. of cases. If over-anxious he should receive phenobarbitone, ½ grain (30 mg.), or amylobarbitone, ¾ grain (50 mg.), twice daily, and tension may be reduced with meprobamate, 400 mg., three times a day. Peripheral vasodilators have been tried but it has been shown recently that β-pyridyl carbinol (*'ronicol'*) has no effect on the growth of hair in alopecia areata, male baldness or diffuse hair-thinning in women. Cortisone by mouth has caused regrowth of hair in cases of alopecia areata, totalis and universalis, but the hair comes out again when therapy is stopped and the dosage necessary is far too dangerous for long-term use. There may, however, be a case for the short-term administration of steroids in a rapidly extending alopecia.

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NOTES AND QUERIES

Winter Resorts for Asthma

QUERY.—Could you please recommend a resort to which I could send a patient with bad asthma for, say, a month in winter?

REPLY.—To recommend a suitable holiday resort for an asthmatic in winter it is necessary to have some knowledge of the underlying factors causing attacks. When emotional factors are playing a part, the choice of a holiday companion is perhaps more important than the locality. If allergy predominates, clear air and dust-free bedrooms are important, and the Swiss mountains probably offer the most favourable conditions: for these cases the Mediterranean islands, and the warm coastal resorts of Southern England in Somerset and Devon appear to be unfavourable. If low-grade infection is playing an important part, the south coast of France, Bournemouth or the Bahamas offer good prospects of recovery. Travelling is best done by air both because of the freedom from effort and discomfort, and because the risk of acquiring fresh infections while travelling is minimized. Air travel is in itself good for most cases of asthma.

R. S. BRUCE PEARSON, D.M., F.R.C.P.

Tetanus Immunization

QUERY.—I should be grateful for the following information:—

(1) Is there any contraindication to the use of tetanus toxoid, or danger in its use?

(2) In particular are (a) previous sensitivity-reaction to A.T.S., (b) an allergic history such as asthma or urticaria, indications to give tetanus toxoid (rather than contraindications)?

(3) After initial immunization with toxoid in either infants (perhaps with diphtheria toxoid and whooping-cough vaccine) or adults what should be the programme of reinoculation?

REPLY.—(1) There is *no* contraindication to giving tetanus toxoid, as reactions following its use are so infrequent and mild.

(2) A history of serum allergy, asthma or urticaria is an indication to immunize actively with toxoid and thus to obviate the emergency

use of antitoxic serum for prophylaxis or therapy. Allergic patients should receive, purely as a precautionary measure, a reduced dose (e.g. 0.1 ml.) of toxoid, followed after some hours, or the next day, by the ordinary dose of 1 ml. if no symptoms have occurred. Both these doses are given deep subcutaneously or intramuscularly. The subcutaneous injection of 0.5 ml. of 1:1000 solution of adrenaline, repeated if necessary, may confidently be expected to control any allergic reaction—a most unlikely event with toxoid, even in a patient with a history of severe asthma.

(3) Reinoculation of tetanus toxoid is advisable after 6 to 9 months, and thereafter at intervals of four or five years. It is not yet known how long one should continue to give boosting doses at these wide intervals in order to ensure life-long protection. An additional boosting dose of tetanus toxoid may be needed after a dirty cut, unless a full primary course, plus adequate boosting dose, have been given and the last injection has been less than, say, eighteen months before. In this connexion patients or their parents must be asked to safeguard a permanent record card of inoculations, which, so far as possible, must be readily accessible when required.

H. J. PARISH, M.D., F.R.C.P.ED.

Virus Immunity

QUERY.—In the case of the various viral infectious diseases of childhood, e.g. measles.

(1) During an epidemic do immune adults carry the virus and should they be regarded as possibly infectious?

(2) Are children incubating the disease infectious during the whole quarantine period?

(3) At non-epidemic times is there any of the virus at large in the community or is it completely absent?

REPLY.—It is not possible to give precise answers to these important and interesting questions. Of the many difficulties which preclude a complete picture of the behaviour of these viruses, mention must be made of the failure until recently to grow in the laboratory those causing measles, German measles and chickenpox. The possibility of demonstrating them by culture in human or monkey tissue has now been realized but even with those which multiply readily in fertile eggs (e.g. mumps, influenza, smallpox) the chance of detecting a very small amount in the throat of a healthy person must be slender. Such answers as can be given to general questions of this sort must therefore depend upon inference and analogy rather than objective support.

(1) The lasting immunity which results from these virus infections is believed by many to depend upon a continued but quiescent infection by the causal agent. There is evidence that infection, and immunity, may be acquired without the development of clinical illness. Immune adults may therefore be persistent carriers of virus regardless of epidemic incidence of the disease, but it is probable that this state usually involves no risk to others since the virus is present in small amount in deeply sited cells —perhaps in the spleen or bone marrow. They are, in other words, closed carriers. With viruses such as measles or mumps, which do not vary immunologically, it seems very unlikely that immune adults would support even a transitory upper respiratory infection transmissible to susceptible individuals but infection of the non-immune may take a subclinical form, and prove infectious to others. Mechanical transfer through contamination of hands and clothing is a quite different possibility and depends upon the amount of virus discharged from a patient and its ability to survive outside the body: knowledge of this property is mainly very incomplete.

(2) The portal of entry in most of these virus infections is respiratory. At first the virus multiplies in the superficial cells of the epithelium and during incubation an increasing amount of it is being built up largely in other tissues. Presumably some of the cells lining the upper respiratory tract are infected throughout the incubation phase but the amount on the mucosal surface is then probably very small. This, together with the absence of respiratory symptoms at that time, must limit considerably the chances of transmission to others—by contrast with the state of affairs at the start of the clinical illness. Although the incubation period for 'pharyngoconjunctival fever' is only about five days, it is noteworthy that recent observations (Roden, A. T., Pereira, H. G., and Chapromiere, Donna, *Lancet*, 1956, **2**, 592) on human volunteers showed that A.P.C. virus could not be demonstrated in garglings collected two days after experimental infection of the throat but some were positive at 4 and 6 days.

(3) Since virus is not regenerated to start a new epidemic, it must be 'at large' in a restricted way in non-epidemic times. Its presence may be revealed by the occurrence intermittently of a few cases or concealed in the minor forms of illness which escape recognition.

PROFESSOR C. F. BARWELL, M.D.

Endocrine Imbalance and Homosexuality

QUERY.—Is there any known relationship between homosexuality and endocrine dysfunction? Is there any biochemical means of measuring such hormonal imbalance and is there any authoritative literature on the subject?

REPLY.—Although the opinion was firmly expressed by Krafft-Ebing (1892) that homosexuality, and various other disorders of sexual behaviour, are due to endocrine imbalance, whilst many others writing after him have held the same views, it can be stated quite categorically that no convincing demonstrations of such hormonal imbalance have been forthcoming. Moreover, many students of the subject have taken precisely the opposite view, namely, that homosexuality, and other disorders of sexual behaviour, are the results not of endocrine disturbance, but of psychological maladjustments. The question was discussed in an article in *The Practitioner* by Swyer (1954), to which the reader is referred for further reference.

The most recent contribution to the literature on hormone excretion studies in patients with anomalies of sexual behaviour has been made by Garrone and Mutrux (1956). These authors have demonstrated convincingly that the urinary steroid excretion (they determined total 17-ketosteroids and their different fractions, 3-α-steroids, formaldehydogenic corticoids, 'total corticoids' and 17, 21 - dihydroxy - 20 - ketosteroids) in a group of 50 patients was no different from that of normal men of comparable ages. There seems no reason to doubt that homosexuality has, in general, no endocrine basis. The one possible exception to this conclusion is the rare case of passive homosexuality in a eunuchoid; in such cases alone may hormone therapy bring about a reversal of sexual outlook.

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G. I. M. SWYER, D.M., M.R.C.P.

Care of Children in West Africa

QUERY.—A patient, whose husband is thinking of applying for a post in the Gold Coast, has asked my advice on the following points and I should be grateful for guidance and information.

(1) She has at present two children, aged two years and three months, and is anxious to know whether the climate would affect them disadvantageously over a period of years.

(2) Is it possible to get adequate supplies of fresh fruit, milk, and vegetables?

(3) She is Rh-negative and her husband is Rh-positive. Whilst no antibodies were found in her second pregnancy, she wants to know whether if this did happen in a subsequent pregnancy there would be facilities for exchange transfusion, should this be necessary? Also whether as a general rule Europeans are advised to return to this country for confinements?

REPLY.—It can be confidently asserted that climate *per se* does not adversely affect the growth and development of children. Many thousands of European children have been brought up in the tropics, including West Africa, and have suffered no ill-effects. In West Africa educational facilities are inadequate for European children over the age of 10 years; at that age it is usual to send them to school in this country.

Fresh fruit and vegetables are in plentiful supply throughout West Africa, but fresh milk can only be obtained in certain localities. Dried or evaporated milk is usually used as a substitute and the makers' claims regarding the excellence of these products are fully borne out by experience of those who use them in West Africa.

It is not the general rule for Europeans to return to Europe from West Africa for confinements, although a considerable proportion of them do so. If there is any question of an exchange transfusion being necessary, it is strongly recommended that arrangements should be made for the confinement in the United Kingdom. The technique of exchange transfusion is not yet in use in West Africa.

PROFESSOR A. W. WOODRUFF, M.D., F.R.C.P.

PRACTICAL NOTES

Eczema of the Eyelids

DURING the five-year period, 1951-55, 238 cases of eczema of the eyelid were seen in the dermatological department of Moorfields Hospital, and these constituted 20% of the total cases seen. In an analysis of these cases, Peter Borrie (*British Journal of Ophthalmology*, December 1956, **40**, 742) draws attention to the fact that 68 of them (29% of the entire series) were cases of dermatitis medicamentosa. Nearly two-thirds of this group (42) were due to penicillin (in the form of cream rather than drops) or sulphacetamide. This is described as 'being in keeping with dermatological experience, local penicillin and sulphonamide therapy having long been abandoned'. Treatment consisted of bland therapy. The few cases with gross secondary infection were treated with 0.5% neomycin ointment. Neomycin is 'recommended for the routine treatment of staphylococcal infection of the eyelids. It is quite as effective as the other antibiotics, very rarely sensitizes, and is never used systemically, so that if resistant strains of bacteria result from its use this will not affect

future systemic antibiotic treatment'. The third largest group was that due to contact dermatitis. Of the 47 cases in this group, five were due to cosmetics (including one due to nail varnish and one due to a man using his wife's face cream). Treatment in this group consisted of removing the causative factor, and local application of 0.5 to 1% hydrocortisone ointment. In the presence of secondary infection, this was replaced by a mixture of 1% hydrocortisone and 0.5% neomycin ointments. There were 12 cases of suspender dermatitis (nickel sensitivity). None of these associated the eyelid condition with that under the brassière, suspender or buckle. Here again the local application of hydrocortisone ointment proved beneficial. The largest group was that of infective dermatitis (77 cases). Treatment consisted of neomycin ointment followed by, or combined with, hydrocortisone ointment. Hydrocortisone ointment also proved useful in the treatment of the 14 cases of neurodermatitis.

Cancer and Achlorhydria

'It seems not unreasonable to accept the presumptive conclusion that in persons with low gastric acidity or pernicious anæmia the probability of occurrence of gastric cancer is greater than in persons with normal acidity'. Such is the conclusion of J. Berkson, M. W. Comfort and H. R. Butt (*Proceedings of the Staff Meetings of The Mayo Clinic*, October 31, 1956, **31**, 583) based upon a 15-year follow-up of 1,058 patients with achlorhydria, 221 of whom had also pernicious anæmia, and whose ages ranged from 30 to 59 years. Whilst the 15-year survival rate was little different from the expected rate, except in the case of males with pernicious anæmia, the number of deaths from carcinoma of the stomach was appreciably higher in the achlorhydric group. The number of deaths from this cause was 26, compared with an expected number of 4.5. In the case of the patients with achlorhydria without pernicious anæmia the number of deaths was 18, compared with an expected number of 3.4, whilst in the case of those with pernicious anæmia the number of deaths was 8, compared with an expected number of 1.1. The recorded number of deaths from carcinoma of the stomach comprised 13% of the total deaths, whereas the expected rate was only 2.3%.

Recording Blood Pressure

It is always recommended that in recording the blood pressure the cuff should be applied evenly and snugly around the arm. If the cuff is applied loosely an erroneous reading will be obtained. W. F. Nuessle (*American Heart Journal*, December 1956, **52**, 905) has investigated the problem in 100 individuals, in whom he recorded the brachial blood pressure with a clip-on cuff applied tightly, and then with the cuff loosened so that its circumference was extended 3.1 cm. He found that in 94 instances higher readings were obtained with the loose cuff than with the tight cuff. The mean increase was 8.1 mm. Hg systolic, and 9.3 mm. Hg diastolic. The difference between the two readings was greater in individuals of average or heavy build (9.8 mm. Hg systolic, and 11.5 mm. Hg diastolic) than in lean persons (5.4 mm. Hg systolic, and 6.5 mm. Hg diastolic). It is suggested that a loose cuff gives high readings because of the central ballooning of the bag, which exerts the pressure effect of a narrow cuff, and it is known that a narrow cuff gives abnormally high readings.

Essential Hypertension in Infancy and Childhood

Taking as their criterion a persistent systolic blood pressure of 130 mm. Hg and a diastolic pressure of 90 mm. Hg as the upper limits of normal, R. J. Haggerty *et al.* (*American Journal of Diseases of Children*, December 1956, **92**, 535) give an analysis of nine cases of essential hypertension in children aged 14 years or less. There were five boys and four girls, and the age at discovery of the hypertension ranged from 7 months to 13½ years. A family history of hypertension was present in five instances. The five patients with severe hypertension (160/110 mm. Hg or above) ranged in age from 7 months to 12 years, all had symptoms attributable to their hypertension and all showed evidence of secondary vascular changes. In only one was there a family history of hypertension. The remaining four patients were all aged 9 years or over when the hypertension was discovered, and all were 'singularly symptom free'. All had 'a strong family history of essential hypertension'. Stress is laid upon the importance of excluding other causes of hypertension, such as renal disease, phæochromocytoma and coarctation of the aorta, before making a diagnosis of essential hypertension in children.

The basis of therapy has been a barbiturate, weight reduction in the obese, and superficial psychotherapy. Restriction of physical activity has been found harmful rather than helpful except in the presence of symptoms such as headache or dyspnœa, and participation in competitive games has been discouraged. The children with mild hypertension (under 160/110 mm. Hg) were given a Rauwolfia preparation, starting off with either 0.1 to 0.25 mg. of reserpine, or 1 mg. of 'rauwiloid', thrice daily, and increasing the dose every two to three weeks

until side-effects occurred. The dose was then reduced until side-effects disappeared, and administration continued indefinitely at this level. In those with severe hypertension the Rauwolfia was supplemented by hexamethonium. If this did not prove effective, sympathectomy was performed. This was done in four cases—with benefit in two instances.

Reducing Diets

THE following simple formula is given by R. J. Slonim Jr. (*Journal of the American Medical Association*, November 24, 1956, **162**, 1233) for calculating the caloric value of a reducing diet for a moderately sedentary adult:—

$$C = 11.4\,(7H - 266 - 6L)$$

where C = calories per day; H = height in inches; L = desired loss of weight per month, in pounds.

The bases for this formula are the three following assumptions: (1) The 'ideal' weight for an individual may be calculated by a rule of 110 lb. (49.9 kg.) for a person 5 feet (152.4 cm.) tall, with 5 lb. (2.3 kg.) added for each additional inch. (2) A person who is mainly sedentary requires a daily dietary allowance of 35 calories per kg. body weight to maintain a constant weight. (3) If a person eats more than 35 calories per kg. of his ideal weight daily he will gain weight at the rate of 1 g. of fat + 1 g. of water for each 9 calories in excess. On these assumptions the ideal diet in calories per day is:—

$$35\left[\frac{5\,(H - 60) + 110}{2.2}\right]$$

The pounds of fat and water lost per day are converted to calories lost per day by the equation:—

$$\frac{L \times 9 \times 1000}{2.2 \times 2 \times 30}$$

The difference between these two equations gives the required number of calories:—

$$C = 35\left[\frac{5\,(H - 60) + 100}{2.2}\right] - \frac{L \times 9 \times 1000}{2.2 \times 2 \times 30}$$

This equation can be further simplified to that given at the beginning of this note. In his article Dr. Slonim includes a nomogram, based upon this formula, which simplifies the calculation of reducing diets still further.

Chlorpromazine and Agranulocytosis

'CAREFUL clinical and laboratory observation of patients receiving chlorpromazine is essential to prevent occurrence of agranulocytosis', according to G. Schick and J. Virks (*New England Journal of Medicine*, October 25, 1956, **255**, 798). This conclusion is based upon their experience with the drug since 1954 in over 700 mentally ill patients in hospital. During this time they have had 11 cases of obstructive jaundice due to chlorpromazine, one case of agranulocytosis (full details of which are given) and two patients in whom malaise, fever, sore throat with ulceration, and decrease of granulocytes in the peripheral blood appeared. In a review of the literature they have found reports of 21 cases of agranulocytosis associated with chlorpromazine therapy. All were females, and in all but two cases the daily dose did not exceed 320 mg. In all but one instance the drug was given orally. The duration of chlorpromazine therapy ranged from 18 to 67 days, with an average of 43 days. Eight of these cases were fatal, and three of these also had jaundice.

Myotatic Irritability

MYOTATIC irritability is 'dependent on the nutritional status of the patient, and is much more likely to be encountered in males', according to I. A. Short (*Scottish Medical Journal*, December 1956, **1**, 399). He investigated the phenomenon in 527 outpatients whom he classified into four groups according to their habitus: Group 1: obese or well covered. Group 2: average build—no evidence of loss of weight. Group 3: naturally thin—no evidence of loss of weight. Group 4: considerable loss of weight or emaciation. Of the 23 males in group 1, only three had myotatic irritability, compared with 22 of the 23 in group 4. Of the 40 females in group 1, none showed myotatic irritability, and only six of the 18 in group 4 did. Of the entire group of 242 females in the series, only eight showed the phenomenon, compared with 155 of the 285 males. It is suggested that the sign is absent principally where subcutaneous fat is plentiful, and that this may be due to masking of the contraction or to interference with the stimulus to the muscle fibres. This would explain the relative rarity of the phenomenon in women, as subcutaneous fat is much more plentiful in females than in males. In other words, the sign has no clinical significance, and the 'so-called association with pulmonary tuberculosis was merely due to the accompanying cachectic state'.

'*Mondor's Disease*'

IN reporting seven cases of subcutaneous phlebitis of the breast and chest wall, or Mondor's disease as it is sometimes known, P. A. Kaufman (*Annals of Surgery*, November 1956, **144**, 847) gives an account of the salient features of the

disease. It presents characteristically as a slightly tender subcutaneous cord, 15 to 25 cm. in length and 3 to 4 mm. in diameter. The veins most commonly involved are those situated on the anterolateral aspect of the upper portion of the breast, or in the region extending from the lower portion of the breast across the submammary fold towards the costal margin and epigastrium. The cause of the condition is not known. It often appears without any precipitating incident. Not infrequently the patient first notices a slightly tender strand on raising the arms. When associated with severe inspiratory pain it may occasionally produce actual dyspnœa. It occurs in young and middle-aged adults of both sexes, but is more common in women. The process is 'uniformly self-limiting' and usually subsides in a few weeks or months, although an indurated cord may persist for one or two years. There is no effective form of treatment. Antibiotics and anticoagulants have been used but without demonstrable effect. Biopsy should be performed only in those cases in which the possibility of some serious underlying condition, such as malignancy, arises. The prognosis is uniformly benign; no deaths or recurrences have been reported.

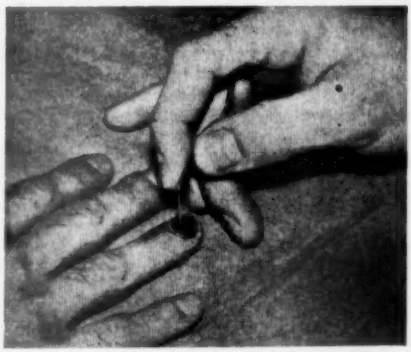
Tuberculosis in Cats and Dogs

THE incidence of tuberculosis in cats is about 2%, according to S. F. J. Hodgman, of the Animal Health Trust Canine Research Station, Newmarket (*NAPT Bulletin*, 1956, **19**, 205), but varies geographically, being largely dependent upon the prevalence of tubercle bacilli in the milk supply. They have a 'formidable resistance' to infection with the human and avian types of tubercle bacilli, but are readily susceptible to the bovine type. Once established in the cat, the disease is widely disseminated and highly destructive. Although there is lack of proved instances of tuberculosis being communicated from the cat to man, the view is expressed that 'the tuberculous cat must be considered as a potential source of infection, especially dangerous to children'. The only safe course, 'and often the most merciful', is to have the tuberculous cat destroyed. The incidence of the disease in dogs is not known. They may be infected by a member of the family with which they live or by contaminated food. Diagnosis may be difficult, but the suggestive symptoms are cough of variable duration and a steady loss of weight. Any dog with such symptoms should be seen by a veterinary surgeon. As in the case of the cat, it is recommended that the infected dog should be destroyed.

In reviewing the general situation, the view is expressed that 'the incidence of tuberculosis amongst both dogs and cats is too low to warrant any decline in the popularity of these useful and almost universal pets'. Although the dog population of the British Isles is numbered in millions, in the course of thirty years of general veterinary practice in small animals the author has only encountered two cases of tuberculosis in the dog. Both were the result of infection acquired by the animal from a human member of the household.

Treatment of Subungual Hæmatoma

A SIMPLE, relatively painless method of dealing with a subungual hæmatoma is described by J. K. Donahue (*GP*, December 1956, **14**, 139). Strict asepsis is essential, but no anæsthesia is required. A paper clip is unfolded and bent to a shape that is easy to hold. The free end is heated in the flame of an alcohol lamp ('a cigarette lighter has been used') until it glows. It is then allowed to cool momentarily. When



the glow disappears it is pushed vertically, with steady pressure, through the nail into the hæmatoma. This is immediately evacuated of blood and the pain is relieved. Two points are stressed. The first is the importance of partial cooling of the end of the clip. If it is used while still glowing 'there is a tendency to incinerate the blood which causes obstruction of the opening'. The second is that steps must be taken to ensure that the tip of the clip is not pushed through so forcibly that it passes through the painless hæmatoma into the very sensitive nail bed. This can be prevented by bracing the hand as shown in the accompanying illustration. Following the puncture, a small piece of tape is placed over the opening for twenty-four hours. The nail is usually not lost, but the opening persists until nail growth allows it to be cut off 'in the usual process of manicure'.

REVIEWS OF BOOKS

Handbook on Poliomyelitis. By JOSEPH TRUETA, M.D., F.R.C.S., A. B. KINNIER WILSON, M.B., M.R.C.P., D.P.M., and MARGARET AGERHOLM, B.M., B.CH. Oxford: Blackwell Scientific Publications, 1956. Pp. vi and 139. Illustrations 31. Price 20*s*.

THIS small book on the diagnosis and practical management of poliomyelitis is written particularly for the general practitioner and the doctor in the infectious disease hospital. Most books dealing mainly with the acute stage of poliomyelitis have an epidemiological and clinical slant. So has this one but it is probably unique in the refreshing anatomico-pathological approach which pervades all its teaching, owing doubtless to the influence of its principal author. That distinguished orthopædic surgeon and original thinker, in close touch with the problems of management of the acute stage, has left his mark here, and the new light shed on old problems is a stimulus to the practising physician. Examples are the clear descriptions of the motor unit, of the mechanics of the respiratory tract, of applied respiratory physiology, and of the principles which should govern the work of physiotherapists and others during recovery and permanent disability.

Another important point is the conservative view taken of tracheotomy. It is for occasional use only, and its disadvantages, here clearly set out, should be ever present in the minds of those responsible for the management of respiratory complications. Muscle charting and training, rehabilitation, the technique of the heated pool and cognate subjects are dealt with in masterly fashion.

There are very few grounds for criticism. The negative aspects of gamma globulin prophylaxis and of quarantine for contacts are understated or omitted. The exceedingly efficient new intermittent positive-negative pressure respirators, with their useful attachments for suction, alveolar-air sampling and spirometry, are perhaps too recent developments to have been dealt with at the time of writing.

Pediatrics. Edited by DONALD PATERSON, M.D., and JOHN FERGUSON MCCREARY, M.D. Philadelphia: J. B. Lippincott Co.; London: Pitman Medical Publishing Co. Ltd., 1956. Pp. xvi and 654. Figures 192. Price £5 10*s*.

PROFESSORS PATERSON AND MCCREARY with their collaborators, all but one now working in Canada, have done for pædiatrics in that country what 'Garrod, Batten and Thursfield' did in Great Britain over forty years ago. By using double columns and frequent passages in small print they have packed a vast amount into just over six hundred pages of text. It is said to be intended for those in general practice with the stress on diagnosis and treatment, but in fact it goes well beyond this in detail. Sampling shows a remarkable evenness of style, indicating skilful editing, and there are several useful appendices on drugs, normal values and diet. The publishers' blurb on the 'up-to-the-minute' nature of the work provokes the reviewer to find fault and therefore it must be stated that there are improved methods of collecting urine from boy babies not involving a breakable test-tube and that there is no clinical account of hypercalcæmia. Denis Browne should have received credit for his views on the mechanical effects of malposition *in utero*.

Dermatology. By DONALD M. PILLSBURY, M.D., D.SC.(HON.), WALTER B. SHELLEY, M.D., PH.D., and ALBERT M. KLIGMAN, M.D., PH.D. Philadelphia and London: W. B. Saunders Co., 1956. Pp. xix and 1331. Figures 564. Price £7 7*s*.

THIS newcomer to dermatological literature has one outstanding virtue. It differs from many other textbooks in that the three authors have recorded clearly and readably their own personal views and philosophies on all aspects of dermatology. It is no re-hash of older textbooks. In fact, it might be called 'Dermatology with the New Look'. Vague terms and obsolescent synonyms are omitted, to the relief, surely, of most readers. The authors state that 'at least a third of the terms ordinarily found in inclusive dermatological texts have escaped mention'. This has helped to provide more space for applied physiology, psychiatry, associated systemic findings, genetics, and other important subjects.

The work is rightly called 'dermatology', dealing as it does with the skin in health and disease. The five main sections deal with basic principles, allergy, diagnosis, therapy, and cutaneous medicine—a term which conveys well the desire to integrate dermatology with 'internal' medicine. Chapters on the fundamentals of cutaneous mycology and bacteriology provide up-to-date reviews on these topics. The chapter on hereditary cutaneous disorders contains an informative introduction on clinical genetics. In the preface, the authors state that they have 'found it impossible to maintain an attitude of consistent solemnity in respect of the subject matter in hand'. Presumably, these remarks refer to the use of cartoons to show the factorial

causation of such conditions as contact dermatitis, nummular dermatitis, seborrhœic dermatitis, and acne vulgaris. These cartoons are original and faintly amusing, but sometimes obscure. For example, the strato-cumulus cloud-like mass hovering over nummular dermatitis has the sinister appearance of an H-bomb spill-out but is presumably intended to show the fog of ignorance regarding the etiology of this condition.

This book is a first-class and authoritative source of knowledge whether the reader wants a single fact or a considered opinion on a broad topic.

Head Injuries and their Management. By FRANCIS ASHBURY ECHLIN, M.D., C.M., F.A.C.S. Philadelphia: J. B. Lippincott Co., 1956. London: Pitman Medical Publishing Co. Ltd., 1957. Pp. x and 127. Figures 10. Price 24*s.*

THE treatment of severe head injuries has suffered during the present century from a number of fashions regarding such matters as dehydration and when to operate. In these respects, this small book from the United States is thoroughly sane and practical, and will be found most useful by the general surgeon who deals with these cases. In the United States, however, these cases are evidently still being transported in the supine position, which is now thought to be undesirable owing to the danger of inhaling secretions or vomit.

Progress in Hematology, Vol. I. EDITED BY LEANDRO M. TOCANTINS, M.D. New York and London: Grune and Stratton Inc., 1956. Pp. ix and 336. Illustrated. Price $9.75.

As indicated by the title this is a review of recent work in the field of blood diseases. It consists of sixteen chapters on various subjects, each written by different authors. With the exception of the British authors, Ungley and Thompson, who have written the first chapter entitled 'Gastric Intrinsic Factor and Vitamin B_{12} Interrelationships', all the remaining contributors are American. A wide variety of topics is covered, including such subjects as parenteral iron therapy, radioactive phosphorus in the treatment of polycythæmia, thrombocytopenias, surgery of hæmophilia, fibrinogen deficiencies, and chemotherapy of leukæmia. The standard of writing and of production is excellent, and many of the chapters are illustrated with excellent graphs, diagrams, and photographs. Adequate bibliographies are appended to each chapter.

The book can confidently be recommended to all who are interested in hæmatology but more especially to those whose work lies in the clinical applications, for the emphasis is on the practical rather than the theoretical aspects of the subject. The physician having to deal with patients suffering from blood diseases will find this book a reliable and very readable source of information.

Interesting Cases and Pathological Considerations. By F. PARKES WEBER, M.D., F.R.C.P., F.S.A. London: H. K. Lewis & Co. Ltd., 1956. Pp. iv and 77. Figures 5. Price 18*s.* 6*d.*

DR. Parkes Weber's name has stood for decades as a symbol, or even a synonym for a combination of a peerless clinical memory, a connoisseur's love of rare things and keen powers of speculation. Anything from his vast store of knowledge which he commits to paper is read with avidity by those whose interests match his own, however much their ability lags behind. This latest book will be no disappointment as it is full of the type of information and scholarship which is pre-eminently his. Some of the articles have already appeared as original papers in scientific journals, an instance being 'My most Interesting Case' (*The Practitioner*, February 1956), but lose nothing in the re-reading. Others are quite new.

The syndrome to which Dr. Parkes Weber gave the name of Steiner Voerner he now regards as being in all probability due to a serotonin-producing carcinoid tumour, and suspects that some cases of flushing, which he had regarded as examples of the auricular temporal syndrome, had a similar origin. The chapter on 'A Portrait Medal of Paracelsus' gives a fascinating picture of the great 16th century physician, and, together with his 'numismatic suggestion', gives yet another example of the author's diverse interests and his ability to become an expert in many intellectual fields.

The Premarital Consultation. By ABRAHAM STONE, M.D., and LENA LEVINE, M.D. New York and London: Grune and Stratton Inc., 1956. Pp. v and 90. Figures 11. Price $3.

THE premarital examination as a branch of preventive medicine is relatively a modern development and one which has become far more general in the United States than it is in Great Britain. This American book describes the conduct of such a consultation. A young engaged couple, John and Mary, are taken through the various stages of such a consultation. Sexual techniques and contraception are adequately described and the tone of the book

is throughout both sympathetic and helpful.

The reader is left in some doubt as to what should constitute a premarital examination. The authors are obviously not certain in their own minds as to whether certain tests, such as the male fertility test, should be undertaken before marriage, and their doubts are to some extent transmitted to the reader. Nevertheless, this little book should be read by all who are likely to advise and examine those about to be married. The list of marriage laws in the various States which forms an appendix makes fascinating reading and enables the British reader to get a glimpse of the varied communities which make up the United States.

A Manual of Human Anatomy. By J. T. AITKEN, M.D., G. CAUSEY, M.B., F.R.C.S., J. JOSEPH, M.D., M.R.C.O.G., and J. Z. YOUNG, M.A., F.R.S. Edinburgh: E. & S. Livingstone Ltd, 1956. Vol. I: *Thorax and Upper Limb*, price 14*s*. Vol. II: *Head and Neck*, price 16*s*. Vol. III: *Lower Limbs*, price 12*s*. 6*d*.

DISCUSSIONS about the medical curriculum usually centre round the teaching of anatomy. It has been pretty generally agreed that the subject cannot be simplified and condensed, but many have urged that the teaching should be made more logical, and that instruction on the function of a part should be blended with the study of its form. This new work attempts to give expression to the modern outlook. Paragraphs indicating the function of parts come after the dissecting instructions, so that the study of the anatomy of the part is undertaken with some knowledge of its functional implications, and not as a mere exercise of memory. The authors advise that dissection should begin with the thorax, which is therefore described in the first part of volume I. The student thus becomes acquainted early with the heart and lungs, peripheral and autonomic nervous systems, all of which he will meet in the introductory courses in physiology. He also starts with the origin of the great vessels, whose further ramifications he will follow in later dissections.

Unlike many manuals, these volumes are really designed to be carried in the hands, and in grubby hands at that. The covers are of tough and well-varnished cardboard, and, like telephone books, each volume is a distinctive colour. The pages, bound with wire rings through perforations, are designed to stay open and lie flat on a bench beside the dissector. The print is bold. The illustrations are intended to be studied with the text on the page opposite, and they are remarkably clear and free from superfluous captions and arrows. Colour is used freely to give clarity.

These are admirable books. They will prove invaluable to the student starting on his two years' work in the dissecting room.

The Inquisitive Physician. By FRANCIS M. RACKEMANN, A.B., M.D. Cambridge, Massachusetts: Harvard University Press; London: Cumberlege, 1956. Pp. xi and 288. Illustrated. Price 40*s*.

THIS biography of George Richards Minot by his cousin, himself a distinguished alumnus of the Boston Medical School, scarcely does justice to the subject. The story of Minot's application to the treatment of pernicious anæmia of Whipple's experimental work on dogs is well known, but it would be difficult from this biography for anyone who happened to be ignorant of the story to be able to piece it together in a coherent manner. Indeed, the book is more accurately described as a family album of the Minot family, seen against the background of the Boston of the first half of the century. As such it presents an interesting picture of that select society which has contributed so much to the intellectual life of the United States. Minot was a Bostonian of the Bostonians. His life and activities began and ended there, and trips abroad, or even elsewhere in the United States, were made merely from a strong sense of duty. There is something rather charming about this insularity and aloofness so characteristic of these old Bostonian families.

Official History of the Canadian Medical Services 1939-1945. *Vol. I: Organization and Campaigns.* Edited by W. R. FEASBY, M.D. Ottawa: Canadian Ministry of National Defence, 1956. Pp. xii and 568. Illustrated. Price $5.

IN modern times no Governments have shown a higher sense of responsibility for the care of sick and wounded in war than those of the English-speaking countries. This book gives a detailed account of the growth of the Canadian medical services from their minute permanent establishment of 166 all ranks in March 1939 and unfolds the story of their deployment. For the professional reader there is an abundance of technical detail; this, however, does not fog the issue for the layman who will appreciate the vast organization required behind the fighting man if he is to get the best of modern medicine and surgery wherever he needs it.

In the light of recent controversy it is interesting that the single medical corps for all three services before the war very rapidly divided into three separate ones, though the

Dental Corps remained common to all. The land campaigns receive the major attention and the arrangement of maps is outstandingly good. The Royal Canadian Navy has but one short chapter which hardly does justice to its tremendous expansion. The immensity of the British Commonwealth Air Training Plan with its striking rapidity of execution is stressed by the vast needs of its medical organization. To the whole book there is a backcloth of vigour and enthusiasm, characteristic of a young and proud nation, largely free from the fetters of tradition. If all its splendid forces are now dissipated they will at least be constantly remembered by the Pulheems system: a worthy, if rather prosaic, administrative medical legacy.

NEW EDITIONS

A Textbook of Psychiatry, by Sir David Henderson, M.D., F.R.C.P., F.R.C.P.ED., and the late R. D. Gillespie, with the assistance of Ivor R. C. Batchelor, M.B., F.R.C.P.ED., D.P.M., in its eighth edition (Oxford University Press, 35*s*.), has undergone careful revision, particularly in the discussion of etiological problems, and in the chapter on epilepsy. This book has always ranked as the most satisfactory comprehensive guide to psychiatry for the general physician, and in its new edition it maintains its right to this claim. Unlike so many textbooks on the subject, clichés, verbosity and the narrow outlook of the academic psychiatrist are all notable by their absence.

Shaw's Textbook of Gynæcology in its seventh edition (J. & A. Churchill Ltd., 32*s*. 6*d*.) has been revised by John Howkins, M.D., M.S., F.R.C.S., F.R.C.O.G. Although much of the original text has been preserved, Mr. Howkins has successfully brought the book up to date, thus effectively blending Shaw's outstanding powers of exposition with current advances. The main change is the addition of a chapter on tuberculosis of the genital tract. Other sections which have undergone careful revision include that on carcinoma of the cervix, and that on infertility. The illustrations, always an outstanding feature of this book, have also received careful attention, and there are 116 new ones in this edition. Bart's has every reason to continue to be proud of this product of its gynæcological department.

Clinical Laboratory Diagnosis, by Samuel A. Levinson, M.S., M.D., PH.D., and Robert P. MacFate, M.S., PH.D., in its fifth edition (Henry Kimpton, 93*s*. 6*d*.), is an excellent guide to the subject. It covers bacteriology, as well as biochemistry and hæmatology, and there are sections dealing with tropical diseases and forensic medicine. Each chapter is introduced by a short review of the relevant physiology and biochemistry, so that the reader can understand the significance of the results obtained by the various techniques described. It is too detailed for the medical student in this country, but is an admirable reference book for him, as well as for the clinician. For the trainee clinical pathologist or biochemist, it can be unreservedly recommended.

Orthopædic Nursing, by Mary Powell, S.R.N., M.C.S.P., Orthopædic Nursing Certificate, second edition (E. & S. Livingstone Ltd., 27*s*. 6*d*.).—This excellent book describes and illustrates the essential bases of orthopædic surgery. The second edition brings up to date the principles and procedures described in the first. It is a little larger and more amply illustrated, but naturally enough, since basic principles have not changed in five years, the essential material in the book is the same as the earlier edition. It is a little disappointing that criticisms of the first edition appear to have been ignored: there is still no place in the index for anterior poliomyelitis; and although the book is much concerned with splints the precautions necessary for the safe use of the Thomas splint have not been amplified and are not adequate; the value of using suitable splints instead of plaster of Paris in the treatment of Colles' fracture is still not mentioned. But the book as a whole is so good that it is invaluable to anyone interested in orthopædic surgery.

Surgeons All, by Harvey Graham, M.D., in its second edition (Rich & Cowan, 25*s*.) has had a chapter added, 'Postscript 1939-1956', which brings it up to date. It is a masterpiece of condensation, and an outstanding example of how medical history can be written in an attractive manner without any sacrifice of accuracy or perspective, and without the use of too many technical terms. In other words, this is a book which will appeal to the layman as well as to the doctor. It gives a superb picture of the development of surgery from ancient times, and as such should be compulsory reading for every medical student—having first been read, of course, by his teachers.

BINDING CASES

Binding cases for this and previous volumes are available in green cloth with gilt lettering, price 5*s*. 6*d*. each post free. The cases are made to hold 6 copies after the advertisement pages have been removed; they are not self-binding. Alternatively, subscribers' copies can be bound at an inclusive charge of 13*s*. 6*d*. per volume; this includes the cost of binding case and return postage.

The contents of the March issue, which will contain a symposium on 'Gynæcology' will be found on page A108 at the end of the advertisement section.

Notes and Preparations see page 263.
Fifty Years Ago see page 267.
Motoring Notes see page A75.
Travel Notes see page A79.

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NOTES AND PREPARATIONS

NEW PREPARATIONS

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'AMENORONE FORTE' tablets each contain 50 mg. of ethisterone and 0.05 mg. of ethinylœstradiol and are intended for use in amenorrhœa of recent origin and as a pregnancy test. Available in boxes of 3 tablets. (Roussel Laboratories Ltd., 847 Harrow Road, London, N.W.10.)

'ASMACORT' tablets each contain prednisone, 1.5 mg.; ephedrine hydrochloride, 15 mg.; theophylline, 120 mg.; and phenobarbitone, 10 mg., and are intended for the treatment of asthma of 'moderate severity and between attacks'. Available in bottles of 20 and 100 tablets. (Roussel Laboratories Ltd., 847 Harrow Road, London, N.W.10.)

'CORTISPORIN' is a new antibiotic ointment, each gramme of which contains 5000 units of 'aerosporin' brand polymyxin B sulphate, 400 units of bacitracin, 5 mg. of neomycin sulphate, and 5 mg. of hydrocortisone (free alcohol), in a petrolatum base, and is intended for the treatment of bacterial infections and inflammation of the skin, the eye and the external ear. It is said to have an antibacterial range 'greater than that of any single antibiotic' and to be 'successful even against *Ps. pyocyanea* and *Proteus vulgaris*'. Skin sensitization and bacterial resistance are 'unlikely' and 'there is no likelihood of cross-sensitization or cross-resistance to other antibiotics'. Issued in tubes of 10 g., with special nozzle. (Burroughs Wellcome & Co., 183-193 Euston Road, London, N.W.1.)

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'SIGMAMYCIN' is a combination of tetracycline and oleandomycin. Its therapeutic range is similar to that of tetracycline, 'but the addition of oleandomycin gives enhanced activity against such gram-positive bacteria as staphylococci, pneumococci and streptococci'. Available in capsules of 250 mg., in bottles of 16 and 100. (Pfizer Ltd., 137-139 Sandgate Road, Folkestone, Kent.)

PHARMACEUTICAL NOTES

BOOTS PURE DRUG CO. LTD. announce that their prednisolone preparation, 'delta-stab', is now freely available in tablets of 1 mg. and 5 mg. Issued in bottles of 30, 100 and 500. (Station Street, Nottingham.)

PFIZER LTD. announce that their prednisolone preparation, 'deltacortril', is now freely available in tablets of 1 mg. (in packs of 100) and 5 mg. (in packs of 10, 20, 100, 500 and 1000). (137-139 Sandgate Road, Folkestone, Kent.)

FILM NEWS

La Presse Médicale announce that their 'annual prize for medico-surgical cinema', comprising 100,000 Fr. (which may be divided) and various other prizes, will be awarded during the last session of the course of 'Actualités médico-chirurgicales' to be held in Paris in March 1957. Any 16-mm. film which is not subsidized and not produced by a laboratory or firm may be submitted. The latest date for receipt of entries is February 28, 1957. Full details may be obtained from the Secrétariat, *La Presse Médicale*, 120 Boulevard Saint-Germain, Paris VIe, France.

The Technique of Intramuscular Injection. This brief film strip, in colour, and the accompanying commentary describe the technique of giving an intramuscular injection. The pictures are clear, and excellent for teaching student nurses although the practice of injecting a standing patient is not to be commended. The commentary is less attractive, and sister tutors will probably prefer to speak spontaneously—and much more naturally. Copies of the film strip and commentary may be obtained free from Benger Laboratories Ltd., Holmes Chapel, Cheshire.

FORTHCOMING CONFERENCES

The Chronic Rheumatic Diseases will be the subject of a 'concentrated week-end course', with lectures, ward rounds and practical demonstra-

tions, to be held at the Rheumatism Unit of St. Stephen's Hospital, Fulham Road, Chelsea, London, S.W.10, on Saturday and Sunday, March 9 and 10, 1957. Full details may be obtained from the Secretary, Fellowship of Postgraduate Medicine, 60 Portland Place, London, W.1.

The Annual Conference of the National Association for Mental Health, the subject of which will be 'The Maladjusted Child', will be held at Church House, Westminster, London, S.W.1, on April 11 and 12, 1957. Full details may be obtained from The National Association for Mental Health, Maurice Craig House, 39 Queen Anne Street, London, W.1.

The *Harvey Tercentenary Congress* will be held at the Royal College of Surgeons in London, from June 3 to June 7, 1957, inclusive. The main theme will be 'A review of the present knowledge of the circulation'. The congress will be followed by a week-end conference, on the more personal and biographical aspects of William Harvey's life, at his birthplace, Folkestone, Kent, on Saturday, June 8, 1957. Further details and application forms for membership may be obtained from the Congress Secretary, 11 Chandos Street, Cavendish Square, London, W.1.

POSTING PATHOLOGICAL SPECIMENS

We have been asked to draw the attention of readers to the need for care when transmitting pathological specimens through the post. The Post Office allows such specimens to be sent by letter post provided they comply with rules which are laid down in a leaflet entitled 'Deleterious liquids or substances. Articles sent for medical examination or analysis', copies of which can be obtained from any post office. Occasionally, pathological specimens are sent through the post so badly packed or sealed that leakage occurs, constituting a real risk to the postal staff and contaminating other mail. It is pointed out that particular care is required in giving detailed instructions to patients who are given receptacles for specimens to be returned by them through the post.

GENERAL PRACTICE AND THE UNDERGRADUATE

A survey published by the British Medical Students' Association shows that organized tuition in general practice is now provided in 22 of the 27 medical schools in the United Kingdom which offer facilities for clinical study. This shows a most commendable increase since 1953, when there were only 10 schools providing such teaching. The five schools in which there is no organized general practice tuition are those of the Middlesex, St. George's, St. Thomas's, and the West London Hospitals, and the Queen's University of Belfast. In those schools which provide tuition in general practice the schemes can be divided into four categories:—(a) 'Health centre' schemes operated by the University authority providing teaching for students. There are only two of these—in Edinburgh and Manchester. (b) 'Residential' schemes, in which the student spends some time living with the general practitioner. (c) 'Attachment' schemes, in which the student is attached to a general practitioner in the mornings for a given period of time, usually one to two weeks. (d) 'Day visit' schemes, in which the student spends a day with a general practitioner.

CLEAN AIR ACT

The New Year has seen the coming into force of certain of the provisions of the Clean Air Act, 1956. These include the provisions enabling local authorities to create smoke control areas, in which the emission of smoke from buildings will be an offence. In such control areas, grates and other appliances in which smokeless fuels cannot be burnt satisfactorily will have to be altered or replaced. Other provisions which have now come into force empower the Minister of Housing and Local Government to make regulations requiring furnaces to be fitted with smoke density meters, and all new furnaces, other than small domestic boilers, must be, so far as practicable, smokeless. The height of new chimneys, other than those of houses, shops and offices, will require approval by the local authority. Local authorities are now empowered to make by-laws requiring the provision in new buildings of such arrangements for heating and cooking as are calculated to prevent, as far as practicable, the emission of smoke.

RAIL TRANSPORT FOR PATIENTS

The Department of Health for Scotland has issued a letter, reminding regional ambulance committees of the advantages of sending patients, who have to travel long distances, by rail instead of by ambulance. Not only does this save petrol, it is often more comfortable for both sitting and stretcher patients. Arrangements between the ambulance service and the railway authorities allow compartments to be reserved exclusively for patients and, if necessary, their escorts. Such patients are taken by ambulance to the station and are met at the other end by ambulance. Provided a patient comes 'within the category of an ambulance case', the entire arrangement for train-ambulance journeys becomes the responsibility of the ambulance service; this includes the cost of tickets for the patient and

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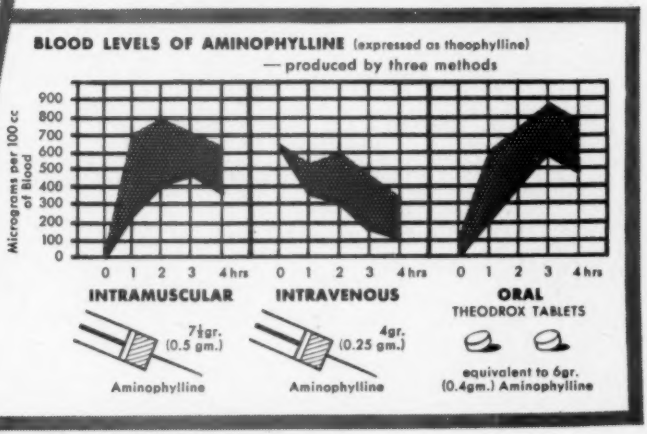

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'Theodrox' tablets each contain gr. 3 aminophylline, and both forms of 'Theodrox' are available in bottles of 25, 100 and 1,000.

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if necessary on medical grounds, for an escort. All the general practitioner needs to do is to inform the ambulance service that travel by train would be suitable.

FACTORY ACCIDENTS

In 1955, the accident rate in factories was the lowest yet recorded, according to the annual report of the Chief Inspector of Factories: the accident index was 89.2 (1950 being taken as 100). The number of accidents increased to 188,403, compared with 185,167 in 1954—an increase of 1.2%, but the factory population increased by 2.5%. The number of deaths was 703, compared with 828 in 1951. The accident rate was about 26 per 1000 for men, and about 10 per 1000 for women. There were 583 (20 fatal) cases of industrial poisoning and diseases, compared with 483 (15 fatal) in 1954. Chrome ulceration accounted for the highest number of cases (261), followed by epitheliomatous ulceration (211, with 18 deaths). There were 69 cases of lead poisoning, and for the sixth successive year there were no fatal cases. There were no deaths among the 15 cases of anthrax.

TREATMENT OF RABIES

The third WHO expert committee on rabies, at a recent meeting, confirmed the 'striking effectiveness' of serum plus vaccine in the prevention of persons severely bitten by a rabid animal. It was stressed that it is necessary to give a complete course of vaccine along with the serum therapy. Because of the danger of side-reactions, it is recommended that serum be given only in very severe exposures after testing the patient for sensitivity. A new technique for protecting persons whose occupation exposes them to the risk of bites by rabid animals was described. This consists of providing basic protection by giving very small doses of chicken embryo vaccine, or a few doses of ordinary nerve tissue vaccine, followed by a single booster dose of vaccine after being bitten, instead of the long (14 to 21 days) schedule of inoculations now performed. For the immediate treatment of wounds inflicted by animals suspected of having rabies, immediate cleansing with soap and water is recommended, followed by cauterizing with nitric acid on parts of the body where this can be used without danger. This, in turn, is followed by the injection of serum around the site of the bite.

BOVINE TUBERCULOSIS

Figures just issued by the Ministry of Agriculture, Fisheries and Food show that there are now 6¾ million attested cattle in Great Britain, representing 67% of the total, compared with 60% a year ago. Wales has the best record, with 85% of its cattle attested, followed closely by Scotland with 84%. The figure for England is only 60%.

LUMINOUS CLOTHING

A new type of 'reflective yarn' has been developed for outdoor clothing which glows a bright silver under car headlights, according to a note in the *Connecticut State Medical Journal* (1956, **20**, 901). Garments made of this grey thread look like any other except when viewed from a car at night. Tests are said to have shown that a driver travelling at 30 miles per hour could see a child in 'an ordinary snowsuit' 100 feet away with low-beam headlights, giving him only 2.2 seconds available stopping time. The same garment made with reflective yarn was visible 525 feet away, allowing nearly 12 seconds' margin. The implications from the point of view of road safety at night are obvious.

LONG-TERM PRESCRIBING

The following prescription was received by a pharmacist on Christmas Eve, according to *The Chemist and Druggist*:—

'Tab. alumin. hydrox.
Mitte 150
Sig.: One every two or three years'.

PUBLICATIONS

Clinical Examinations in Neurology, by Members of the Sections of Neurology and Physiology of the Mayo Clinic, covers ground already familiar from similar productions, of which Monrad-Krohn's handbook is probably the most widely used in Britain. As might be expected from its source, it is more frankly physiological in its approach and it also deals clearly and authoritatively with such ancillary methods of investigation as electroencephalography and electromyography. Full of reliable information and advice, it can be strongly recommended to any physician who is called on to carry out neurological examinations. The quality of printing and binding is beyond reproach, and renders the book a pleasure to handle. (W. B. Saunders Co., price 52s. 6*d*.)

Refresher Course for General Practitioners.—Volume 3 of this series consists of a series of specially commissioned articles published in the *British Medical Journal* between April 1952 and September 1953, and fully revised for publication in book form. It contains 60 articles covering a wide variety of subjects, ranging from 'Psychiatric treatment and the law' to 'Recurrent boils'. (British Medical Association, price 25*s*.)

The Complete Cookery Book for Diabetics, by Iris Holland Rogers, of the British Diabetic Association, can be wholly recommended to all diabetics as a reliable and practical guide to the enjoyment of good food. (H. K. Lewis, price 6*s*.)

Expert Committee on Insecticides, Sixth Report, WHO Technical Report Series No. 110, deals with the whole subject of insecticide equipment: specifications, methods of use, and maintenance. (H.M. Stationery Office, price 3*s*. 6*d*.)

Junior Health and Hygiene Manual, by the Medical Officer for St. Pancras, and his deputy, is a wholly successful attempt to provide instruction in healthy living and hygiene for young people. School teachers and club leaders will find it particularly useful, and it will prove most useful to practitioners who are asked to lecture to young peoples' clubs or the senior forms in schools. (The British Red Cross Society, price 2*s*. 6*d*.)

Directory of Contributory Schemes for the Year 1956 is published by the British Hospitals Contributory Schemes Association (1948), Royal London Buildings, Baldwin Street, Bristol, 1. Price 10*s*. post free.

OFFICIAL NOTICES

Prednisone and Prednisolone.—The Ministry of Health, in conjunction with the Department of Health for Scotland and the Ministry of Health and Local Government, Northern Ireland, has made arrangements with U.K. manufacturers for prednisone and prednisolone which will enable preparations of these substances to be supplied on prescription from February 1, 1957.

Remuneration of Chemists.—The Minister of Health has approved the following alterations in the terms of service for chemists:—(a) An additional 1½*d*. per prescription to be paid on all prescriptions, other than those for trusses and hosiery, dispensed during the calendar year 1955. (b) An additional 2½*d*. per prescription to be paid on all prescriptions other than those for trusses and hosiery, dispensed from January 1, 1956.

OFFICIAL PUBLICATIONS

Report of the Ministry of Health for the year ended 31st December, 1955. Part II. On the State of the Public Health.—In this, his annual report for 1955, the chief medical officer of the Ministry of Health notes that for the second year in succession no case of smallpox was recorded. On the other hand, the acceptance rate for primary vaccination of infants is still disappointingly low—varying between 5.1% and 70.1% in different areas. The stillbirth rate—at 23.3 per 1000 total live and still births—has remained relatively stable since 1948, and the view is expressed that 'it is disturbing to find that for seven years there has been no progress in this field that has had any effect on national rates'. Disappointment is expressed at the steady decline in breast feeding, particularly in teaching hospitals. In these the rate was only 67.67%, compared with 76.06% for all infants in institutions, and 82.4% for infants born at home.

There was an increase of 1,245 deaths from cancer: 847 men and 398 women. Carcinoma of the lung accounted for 826 more deaths in men—an increase of 5.9% over the 1954 figure—and for 30.77% of all male cancer deaths. Similar figures for females are 115 more deaths, an increase of 4.9% and representing 5.68% of all female cancer deaths. The view is expressed that 'the practice of those countries abroad which do not countenance smoking in theatres, cinemas or even in public transport is one that deserves at least study, if not imitation'. In both sexes the mortality from leukæmia is now more than twice the figure recorded in 1936. For the first time since 1947 the number of new patients with syphilis attending venereal disease clinics with infections of less than one year failed to fall. The clinic incidence of gonorrhœa in both sexes increased, and 'it is now clear that there has been no appreciable improvement in the control of this disease during the last five years'. (H.M. Stationery Office, price 9*s*.)

The Health of The School Child.—In this, his report for 1954 and 1955, the chief medical officer of the Ministry of Education states that 'the health of the great majority of the children was good'. Only 1.46% of them were considered to be in poor physical condition in 1955, compared with 2.55% in 1952. Child mortality continued to decline. In 1955, 2,755 children, aged 5-14 years, died, compared with 9,047 in 1938. Over this period deaths from tuberculosis fell from 973 to 54, and deaths from diphtheria from 1,733 to five. On the other hand, twice as many children in this age-group now die annually from violence as die from all the infectious and respiratory diseases put together. Although body-lice- and flea-infested children are now rarely found, there are still a quarter of a million children with verminous heads. (H.M. Stationery Office, price 6*s*.)

CORRIGENDA.—In our January issue (p. 7) 'ilotycin' was given as one of the proprietary names for tetracycline. This, of course, is not the case. 'Ilotycin' is the proprietary name of Eli Lilly & Co. Ltd. for erythromycin. The two proprietary names for tetracycline are 'achromycin' (Lederle) and 'tetracyn' (Pfizer).

In table 1 on p. 66 of our January issue, 'ancolan' was given as a proprietary name for phenindamine, whereas it is 'The British Drug Houses' proprietary name for meclozine.

On p. 31 of our January issue it was incorrectly stated that allyl*iso*propylacetylurea contains bromine.

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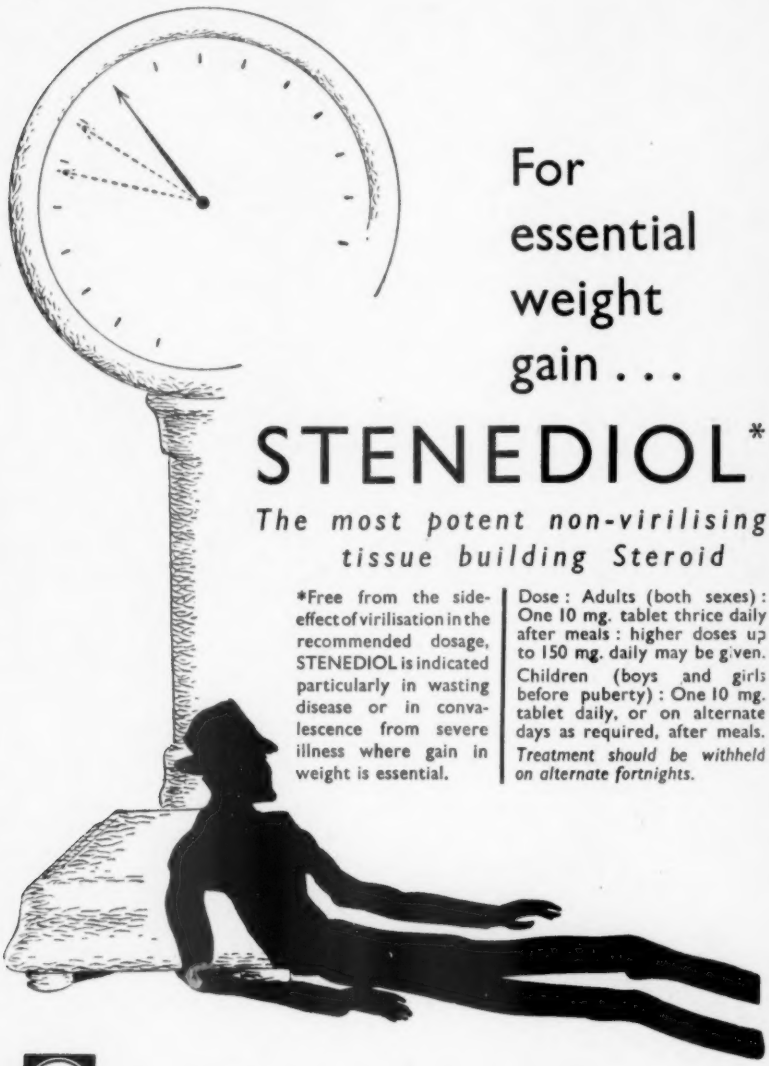

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Dose : Adults (both sexes) : One 10 mg. tablet thrice daily after meals : higher doses up to 150 mg. daily may be given. Children (boys and girls before puberty) : One 10 mg. tablet daily, or on alternate days as required, after meals. *Treatment should be withheld on alternate fortnights.*

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THE PRACTITIONER

Fifty Years Ago

'There is one great difficulty in modern times: the choosing not only what to know but what to trust; what not to know and what to forget'.—John Brown: *Horæ Subsecivæ*.

FEBRUARY 1907

'THE "cancer curer" we have always had with us; we are now suffering from a severe visitation of the "cancer crank" '. By this 'Notes by the Way' mean 'the highly scientific person who, knowing nothing of practical medicine, and indeed often holding it in the contempt naturally born of ignorance, attacks the problem of cancer from a purely biological standpoint, and having satisfied himself that it is all a case of the anomalous behaviour of certain cells, forthwith publishes this as an epoch-making discovery. He then finds something which he persuades himself will eliminate the peccant cell and reduce the anarchy of disease to the order of health . . . The possession of a medical degree, though it may to a certain extent be a test of knowledge, does not necessarily confer wisdom. Men whose academic honours almost exhaust the alphabet are often utterly lacking in judgment and critical power. They allow themselves to be carried away by the wind of every new doctrine, and do infinite harm by premature reports of the virtues of the latest therapeutic novelty. These men are especially apt to be led astray by the cancer crank . . . By all means let trypsin be fully tried, but to vaunt it as a "cure", before anything at all like a cure has been achieved, is a crime against mankind . . . the discovery either of the germ or of the remedy can only be hindered by the premature pæans of frothy enthusiasts'.

'The fishy theory of leprosy', advocated 'with such ability and persistence by Mr. Jonathan Hutchinson in *The Times* and elsewhere, was not of course originated by that distinguished surgeon. It is the oldest theory of all, and had acquired an ancient and fishlike smell that made it stink in the nostrils of the profession till he quickened it into an artificial freshness'.

That ' undue ' noise was already a problem fifty years ago is evident from a comment 'The Noise Nuisance': 'There is, we believe, a society in London which professes to make the abatement of this evil the object of its existence, but we have not observed that its labours have been crowned with any appreciable success. A "Society for the Suppression of Unnecessary Noise" has recently been founded in New York. All this shows that people are becoming restive under an infliction which is becoming more and more a nuisance and a danger'.

Under the heading 'Place aux Dames' the Editor writes: 'One by one the strongholds of medicine have fallen to the conquering blast of the feminine trumpet. Women can now get medical degrees at all Universities except Oxford and Cambridge, over which there still hangs the shadow of an impenetrable conservatism; and they are admitted by all corporations except the London College of Physicians and the English College of Surgeons. The ladies, however, have not fought so strenuous a fight against the forces of prejudice without learning how to carry the warfare to a victorious issue. They are now summoning the fortress of surgery in Lincoln's Inn Fields to surrender. They urge that since they last battered at its doors in 1895, the entry of women into the medical profession has steadily increased, and the total number now on the *Medical Register* is over 750 . . . We think the ladies have made out a good case for themselves, but we cannot feel much confidence that they will succeed in forcing their way into the sacred precincts of the College of Surgeons'.

Sir Raymond Henry Payne Crawfurd, M.D., F.R.C.P. (1865-1938)

The opening article in this number, 'The Treatment of Some of the Forms of Gout', is by Arthur P. Luff, M.D., F.R.C.P., Physician to St. Mary's Hospital. Arthur Pearson Luff,

the centenary of whose birth occurred last November, became lecturer on medical jurisprudence and toxicology at St. Mary's in 1887, assistant physician in 1890, and full physician in 1896. A recognized authority on gout, he enjoyed a lucrative practice, for he was not afraid to treat acute attacks of the disease with morphine, but it is interesting to note that in this paper he states: 'The administration of opium or morphine should, if possible, be avoided owing to the risk of its deficient elimination, and also on account of its diminishing the amount of urine, and its tendency to derange digestion and to check hepatic metabolism'. Archibald Young, M.B., C.M., Dispensary Surgeon, Western Infirmary, Glasgow, describes 'Posterior Tarsal Resection of the Foot by the Method of Mikulicz and Wladimiroff'.

Raymond Crawfurd, M.D., F.R.C.P., Physician to King's College Hospital, discussing 'Tricuspid Stenosis', reports seven cases in which its existence was not suspected. Scholar-physician and administrator, Sir Raymond Henry Payne Crawfurd was born in 1865, was educated at Winchester, Oxford, and King's College, London, and graduated B.M., B.Ch. in 1894. He was elected assistant physician at King's College Hospital in 1898, physician in 1905, consulting physician in 1930, and was knighted in 1933. At the Royal College of Physicians he served as registrar for thirteen years, and he helped to found the Section of the History of Medicine of the Royal Society of Medicine. He died in 1938.

Thomas Lewis, D.Sc., M.B., B.S., Fellow of University College, London, deals with 'The Interpretation of Sphygmograph Tracings, and of Tracings Produced by Compressing the Brachial Artery'. The title of the Prize Essay by G. H. Bate, L.S.A., of Bethnal Green is 'The Relative Value and the Selection of Disinfectants'. The 'hero' of the 'Famous Quacks' series this month is Joshua Ward ('Spot Ward').

Among the books reviewed are Sir Patrick Manson's 'Lectures on Tropical Diseases'; R. Tanner Hewlett's 'Pathology, General and Special, for Students of Medicine'; Osler's 'Æquanimitas' ('couched in terms clear, illuminating, and not infrequently rising to a very high degree of eloquence'); and Alfred T. Schofield's 'Unconscious Therapeutics, or the Personality of the Physician'.

'During the present month Mr. H. K. Lewis will establish his circulating library in more convenient quarters adjoining the old premises at 136, Gower Street'.

According to 'Practical Notes', 'If the rash of measles does not come out well, warm drinks and a hot bath will often hasten its development'.

'Angier's Emulsion', in which the petroleum is 'rendered acceptable to the palate', celebrates its jubilee. W. R. B.

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L. FARRER-BROWN,
Director of the Nuffield Foundation.

BINDING CASES

★ Binding cases for volume 177 (July to December, 1956) and previous volumes are now available in green cloth with gilt lettering, price 5s. 6d. each, post free.

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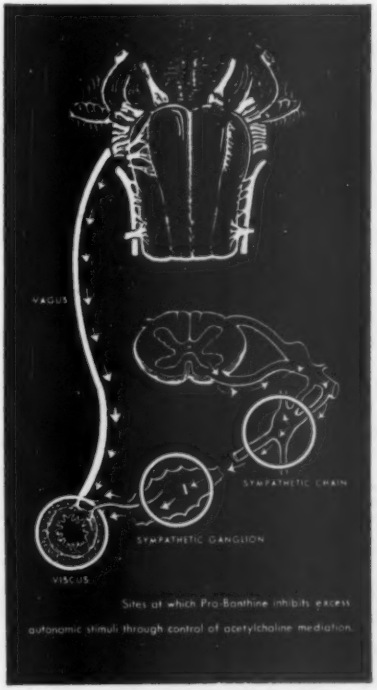

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[1]Gastroenterology (1953) 25 : 416.
[2]Gastroenterology (1953) 25 : 24.

SEARLE

PB : P96

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MOTORING NOTES

A Courageous Experiment

By ROBERT NEIL

STUDENTS of automobile design seldom cease wondering why it is that, despite this country having been among the first to take an active and serious interest in the then new horseless carriage at the turn of the century, fifty years after the start of the industry the most original cars in production should all emanate from countries other than the United Kingdom. Perhaps because of the conservatism of the British people, although there are those who would blame the timidity of the industry's leaders, there is not one single car produced in this country on which the engine, gear-box and transmission are mounted as logic would suggest, i.e. all at one end. It is unimportant at which end. It does seem unreasonable to place the engine at one end—the front—and employ a needless propellor shaft to transmit the power to the rear wheels. The buyer on the Continent can choose from at least five cars which use rear-mounted engines, connected directly to the gear-box and transmission, whilst there is always that exemplary car the Citroen (fig. 1, 2).

THE CITROEN

This well-known French car employs front-wheel drive, with the result that the lack of a transmission shaft beneath the floor allows the car to be built very low without any loss of essential headroom. Readers who have driving experience abroad will confirm that of the thousands of Citroens one sees on the road, a large proportion are driven very hard over even the worst of road surfaces, and it should be remembered that the model which has only just been outdated by the introduction of the new Citroen DS19 was first produced over twenty-two years ago.

This latest Citroen is without doubt the most complicated and advanced car in production today and, although in some details one suspects that the design staff have employed complicated methods because they are complicated, it can in general be described as a courageous and worthwhile experiment. Once one has experienced this car on the road, it is apparent that the standard of passenger comfort and stability granted has not previously been offered anywhere. The car is crammed with interesting features from the narrow air entry at the front, which makes no effort to look other than an air entry, to the rear trafficators, sensibly mounted high on the roof line, where following drivers can see them.

Disc brakes—previously used only on racing or competition cars—are used on the front, and physical effort by the driver is reduced to the minimum by operating them hydraulically. Application of the brakes on any car causes a transfer of weight towards the front, with the result that braking efficiency is reduced on the rear wheels. Because of this the proportion of braking effect passed through the front and rear wheels of the Citroen is varied according to the weight being carried in the car. The clutch is automatically operated, so that the car can be controlled by the accelerator and brake control alone. The steering is power assisted, which also reduces the effort required from the driver.

The most interesting feature of the car is the system of suspension employed; the car is suspended hydropneumatically. Incorporated in the suspension is a device which automatically retains the car on a level keel, and the effect of this in actual use is almost uncanny. Because the car remains level, in spite of the movements of the road wheels, one has the impression that the car is being carried by a giant hand. The action of the levelling device nullifies the effect of dropping, or picking up, even one passenger; if, on halting, an extra passenger is collected the car momentarily sinks slightly, but almost at once resumes its normal level.

One cannot help regretting that this very advanced car should have been built outside the United Kingdom. Apart from any commercial success that may, or may not, be achieved by the production of specially advanced designs the study involved in their design and develop-

FIG. 1.—The latest Citroen DS19. This car employs front-wheel drive and it can be seen that its appearance is strictly functional.

ment will always be beneficial in extracting the best engineers from a money-making rut. Impractical as many of the so-called 'dream cars' built in the United States undoubtedly are, they serve to remind designers that their true function is to explore, rather than to be mere sorters of jigsaws composed of well-known mass-produced components.

DRIVING FAULTS

It has been said elsewhere that if all road users were courteous at all times there would be no accidents. There is much truth in this. Since the petrol shortage began, I had thought that with the diminishing number of cars on the road one would see fewer examples of thoughtless and selfish driving, but I have been disappointed. In the last few weeks I have seen repeated instances of drivers attempting to cut their way through stationary queues waiting at traffic lights, and edging in to the wrong line of traffic in an effort to get nearer the front. The latter practice is especially irritating, as the driver who forces his way up the left-hand lane so often seems to turn sharp right as soon as the traffic starts moving again. Knowing how edgy many of us get, it is little wonder that treated like this a few times one's own driving degenerates. An irritated driver soon becomes an angry driver, and this leads to attempts to do something well beyond his ability, often with results that, in a cooler moment, he would have been the first to forecast. It would be a revealing exercise if all motorists timed themselves over some journey which they do regularly through typical suburban conditions. I would suggest that on the first occasion every reasonable effort—bearing in mind conditions and traffic—should be made to save time, and on the second occasion, after the lapse of a few days perhaps, a real effort should be made to drive gently and sedately all the time. Any driver who attempts this exercise will be surprised at the small margin between his fast and slow runs. This theory can be employed to raise the skill of an average driver.

In the case of a driver of limited skill and experience who desires to become accustomed to driving at high speeds in safety, far the best method is to train himself over a known stretch of road, but instead of attempting to drive thoughtlessly faster than is his normal, he should devote his complete attention to trying to drive much more smoothly. If a conscientious effort is made he will soon discover that he seems to be driving far more slowly than his normal. This is because the effort has been reduced so much, and now is the time to try raising the speed slightly. As soon as he notices, and it will be noticeable, that his driving is becoming rough and graceless, he should again relax enough to regain the previous rhythm. Bearing all this in mind it is not surprising how often the selfish drivers seem to be at the same time relatively unskilled. I have often wondered how these thrusting drivers would get on if they were suddenly given the honour of competing in an important motor race.

FIG. 2.—The immense capacity of the Citroen luggage boot is partially due to the fact that the spare wheel is carried beneath the bonnet, and the luggage boot is extended well forward owing to the absence of a transmission shaft to the rear wheels.

RELIABLE STARTING

I am indebted to a reader of *The Practitioner* for reminding me of a suggestion which would undoubtedly be of value to many readers.

There is now more than one car on the British market on which, in the interests of economy and ease of production, no starting handle has been fitted. Whilst this appears to bring no problems to the average motorist, the constant drain on the battery of a practitioner's car, most of whose motoring is confined to relatively short journeys with frequent restarting, can eventually lead to the battery becoming completely flat. As no starting handle is fitted, this automatically means that one becomes involved in both the delay, irritation and expense of having a tow. A reader who has suffered in this way has cured all his troubles by changing the battery normally fitted to his car for a heavy duty one. Although it would obviously have been better if the manufacturer had done this in the first place, it will undoubtedly be much cheaper and better for any practitioner who runs a car without a starting handle to obtain a heavy duty battery and avoid possible greater expense and trouble later.

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TRAVEL NOTES

The Spas of Germany

By PENELOPE TURING

GERMANY is essentially a land of spas. Some date back two thousand years to the time of those indefatigable bathers the Romans, others have been established quite recently like the delightful Bad Mergentheim just south of Würzburg, where the springs suddenly bubbled up in a season of drought 130 years ago and have now taken the place of Karlsbad with water of the same type, except that the springs of Mergentheim are cold instead of hot.

THE CHARM OF THE GERMAN SPA

The map of Germany is dotted with Bad-this or Bad-that, ranging from large and famous centres to small spas, scarcely more than villages, hidden away among the hills. Since the 1939-45 War nearly all have been reorganized and brought up-to-date, and from the clinical point of view there is a highly efficient organization which publishes a spa calendar and literature on the various treatments available. But German spas are much more than therapeutic centres, for they form a regular holiday way of life, taking the place of our seaside resorts at home.

So far I have not had occasion to take a cure at any of them, but I have a special affection for the spa towns from the mountains of the Harz to the Alpine fringe. The variety is quite fascinating, but I have never yet found one which was sordid. They seem to have a mysterious gift of lifting all holiday makers above the tripper level.

There is a special gaiety and charm, sometimes even elegance, at most spas great and small, and always plenty to do: dancing, racing, swimming, music. Occasionally there are casinos, always the social centre of the Kurhaus, the beautifully kept kurparks where one can wander among the trees or drink coffee or an aperitif at a terrace café as the dusk falls and lights begin to twinkle, and beyond the wider beauties of mountain and valley, the scent of pines or the song of running waters.

THE QUEEN OF GERMAN SPAS

Baden-Baden is the queen of German spas. It remains well known for its rheumatic treatments and so on, but as a holiday centre, naturally one of the more expensive, it provides an almost unique blending of past and present grace. To east and south are the great silences of the northern Black Forest: mile after mile of pine-covered hills and narrow winding valleys with their brilliant green alpine pastures and chattering trout streams. Two famous roads, the upper road (Schwarzwald-Hochstrasse) and the valley road (Schwarzwald Tälerstrasse), take one on a wonderful circular drive from Baden-Baden to Freudenstadt and Gernsbach and show much of the best of this district. In the town there are first-class hotels, gardens, restaurants, some shops which will bear comparison with Paris, and everywhere enchanting vistas of graceful buildings among the trees at all levels, for it is a town of steps and of fountains. The casino is probably the best known in Germany, and its gaming rooms with their brocaded furniture,

FIG. 1.—The market place of Bad Berneck.

great crystal chandeliers and impassive croupiers belong to the elegance of the Edwardian era.

But not everyone wants the royal sophistication of Baden. A few miles to the south is Freudenstadt which, whilst it is not a true watering place, is classed as a climatic health resort which provides, amongst other things, 'after-cure following carbonated baths for cardiac diseases'. This is the complete contrast to Baden. Freudenstadt was badly bombed during the last War, but the picturesque market square, one of the biggest in Germany, has lost nothing in the rebuilding. Round it, under the cream-painted houses with their pointed roofs, is a complete arcade of shops, with gardens in the centre. The Kurhaus—entirely a social centre here—is one of the best examples of modern interior decoration which I have seen anywhere, with delightful restaurants and its own little theatre.

LAKE CONSTANCE

Following the Black Forest south you come at last to the lovely country fringing the German side of Lake Constance. Here, among the warmth and colour of painted houses and baroque churches, there are more spas—Badenweiler at the southern tip of the Forest, and, farther east in the beautiful Allgäu district between the Alps and the Danube valley, Bad Wörishofen. This is one of the better-known Kneipp centres, but from the British tourist's point of view it is almost unknown country. Within easy reach are the lovely old mediæval town of Memmingen, and Ottobeuren—one of the finest baroque abbeys. These and the rolling miles of pastures with their scattered woods and villages, and the grey-brown Allgäu oxen which pull cart or plough make it one of the most picturesque districts in Bavaria.

FIG. 2.—The Sprudelhof, Bad Nauheim.

THE FICHTELGEBIRGE

Away at the extreme north-east corner of Bavaria there is an area of modest mountains and woods, not unlike the Black Forest, called the Fichtelgebirge. Here there is a delightful little spa called Bad Berneck (fig. 1) which is another Kneipp centre. It lies in a wooded valley scattered among the trees, has one excellent hotel, the Bube, and, being only a few miles from Bayreuth, accommodates those visitors to the Wagner Festival in July and August who prefer to stay outside Bayreuth itself.

THE RHINE VALLEY

The middle Rhine valley has some of the most famous of Germany's spas. Wiesbaden has thermal saline springs and as a place has much in common with Baden-Baden: a patrician cachet going back to the days when the Kaiser sometimes conducted the orchestra here in person. Wiesbaden itself is a charming, well-laid-out town, and lying close to the point where the Main joins the Rhine it is an ideal centre for exploring the most spectacular part of the Rhine valley down as far as Coblenz.

A little farther to the north-east is the heart spa, Bad Nauheim, with its three graceful fountains playing in the courtyard of the Sprudelhof (fig. 2); and to the west of this the nose and throat centre, Bad Ems, in the valley of the Lahn, a Rhine tributary. Bad Ems is close to the Rhine and an admirable centre for the wooded hills of the Westerwald and Taunus and some of the best wine-growing districts.

THE HARZ MOUNTAINS

A good deal farther to the north, and just south of Hanover, is the little-known Harz Mountains district, more than half of which is now in the Soviet Zone of Germany. On the western side of this very lovely and unspoilt land of mountain and forest is another of my favourite spas—Bad Harzburg, which until recently was a British Army leave centre. It has now been re-established as a spa for brine baths and Kneipp treatments. There is here the typical German cleanliness, everything is neat and well cared for: the gardens through which runs the river Radau, the winding hill paths which lead one on from seat to seat, and the little cable car which carries one lazily to the top of the valley side where 10 pfennigs (about 2*d.*) in the slot of a telescope will give you a somewhat indifferent view of country beyond the Iron Curtain. There is a delightful casino here, too, where you can eat or drink, dance or give a party, do almost anything in fact—except gamble. Its gaming licence has not yet been re-issued since the war.

With or without a car, collecting spas can make an extraordinarily attractive holiday for, although their name is legion, each one has its own particular character and rather endearing self-importance.

Boat and train journeys via Harwich-Hook of Holland or Dover-Ostend take about 24 hours to Northern and Southern Bavaria, less to the Black Forest, 15 hours or more to the middle Rhine and about 20 hours to the Harz. Fares will be increased slightly from February 1; approximate 1st and 2nd Class returns via Harwich will be: London-Baden-Baden £20, £15 5*s.*; Freudenstadt £20 10*s.*, £15 15*s.*; Berneck £22 10*s.*, £17; Wiesbaden £17 10*s.*, £13 10*s.*; Bad Harzburg £18 5*s.*, £14 5*s.* By air to Cologne (for middle Rhine) B.E.A. 2¼ hours, £20 7*s.* return; Stuttgart (for the Black Forest) Lufthansa 3¼ hours £29 16*s.*; Nuremberg (for Berneck) K.L.M., Lufthansa or P.A.A. 4-5 hours, £29 5*s.*; Hanover (Harz) B.E.A. 3½ hours, £27 18*s.* In May, Lufthansa and B.E.A. will introduce certain cheap night flights which will make a reduction of several pounds on the fare. Spa calendars and technical spa information can be had from the German Tourist Information Bureau, 6 Vigo Street, London, W.1.

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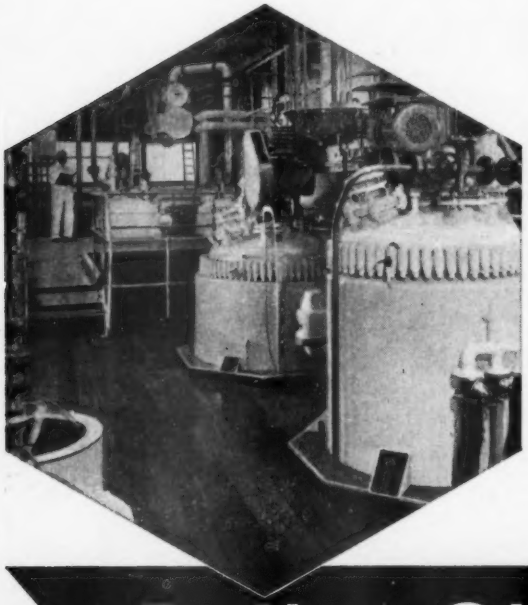

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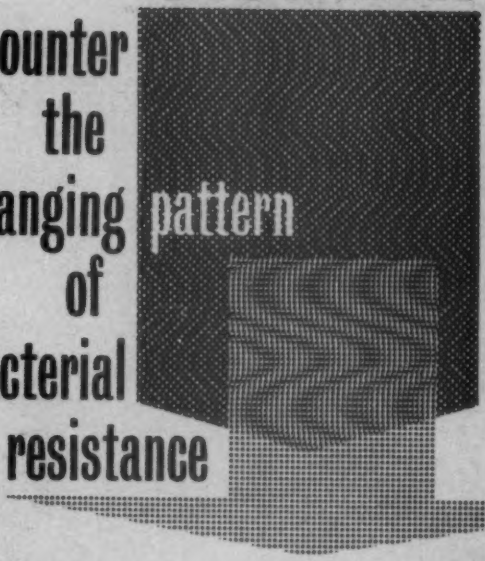

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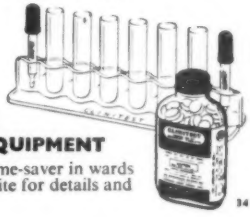

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Save time on urine tests with . . .

CLINITEST and ACETEST

Reagent Tablets
for the detection of Glycosuria

Reagent Tablets
for the detection of Ketonuria

Both tests performed simultaneously in 1 minute!

Specialists, General Practitioners, Clinics and Hospitals in all parts of the country have used and prescribed 'Clinitest' Reagent Tablets since 1947. Many valuable hours have been saved. Now after intensive research work and clinical trials the makers of 'Clinitest' Reagent Tablets have produced 'Acetest' Reagent Tablets for the detection of Ketonuria. With 'Clinitest' and 'Acetest' Reagent Tablets, reliable routine sugar and acetone tests can be carried out *simultaneously* in one minute!

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No external heating • No measuring of reagents

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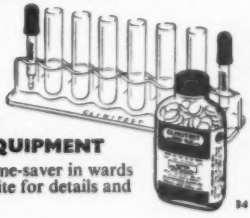

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An invaluable time-saver in wards and clinics. Write for details and hospital prices.

94

The advantages of

ACETEST

Reagent Tablets

Quick and reliable, a single tablet provides all the reagents to perform a test. Low cost permits this tablet test to be used as a screening procedure or as a routine for diabetic patients. No danger of false positives with normal urine. No caustic reagents.

TO PERFORM A TEST:

1. Put 1 drop of urine on tablet.
2. Take reading at 30 seconds. Compare tablet to colour chart provided.
3. Record results as negative, trace, moderate or strongly positive.

Supplied in bottles of 100 tablets with colour scale.

'Acetest' Reagent Tablets *(diagnostic nitroprusside tabs.)* are also available under the N.H.S. on Form E.C.10. Basic Drug Tariff price 3/10 per bottle of 100 tablets (with colour scale).

REFERENCES

(1954) **'Clinical Tests for Ketonuria',** *'Lancet' April 17th, pp.* **801/804**

(1954) *'Medicine Illustrated', May, p.* **289**

(1954) *'Practical Clinical Biochemistry', Heinemann, p.* **74**

(1954) **'Clinical Tests for Ketonuria',** *'Lancet'. July 10th, p.* **95**

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They like Lucozade..

and they can keep it down—

Lucozade has won its place in the sickroom because it is so very palatable. Patients enjoy it and, what is more, they can keep it down even when other food is refused, or vomited. It is difficult to assess the value of Lucozade simply in terms of the glucose it contains. It is the patient's response which is so interesting. Its acceptance so often coincides with a distinct and happy turn for the better, well illustrated in the following brief report:

"My little boy was ill . . . and was completely off his food. I must admit that I only thought of Lucozade at the last moment, after two days of worry, but he improved from the time of taking it."

LUCOZADE

the sparkling glucose drink

REPLACES LOST ENERGY

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Nidoxital
TRADE MARK
CAPSULES
make more mornings
"good mornings"
for patients with
nausea and vomiting
of pregnancy
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Ortho Pharmaceutical Limited
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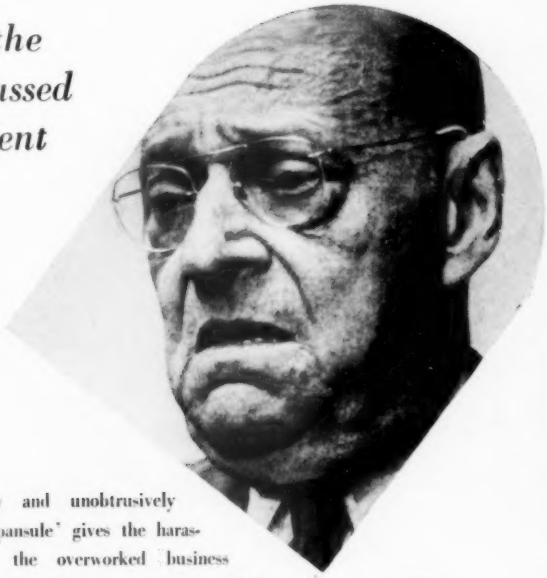
for the harassed patient



Smoothly and unobtrusively 'Drinamyl Spansule' gives the harassed housewife, the overworked business man or the menopausal woman day-long relief from tension—with just one oral dose. 'Drinamyl Spansule' does not tempt the patient to establish the melancholy t.i.d. or q.d. habit of taking 'another pill to keep me going'. Harassment and worry are replaced by a day-long mood of calm composure.

'Drinamyl Spansule' sustained release capsules
Strength No. 1: each capsule contains 10 mg. 'Dexedrine' (dextro-amphetamine sulphate) and 64 mg. (gr. 1) amylobarbitone.
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Both strengths in containers of 30 capsules

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SUDLP66 (col)

THIS CHILD is suffering from acute otitis media. The parents are anxious. Inflammation and pain must be relieved and infection controlled.

A CLEAR CASE FOR AURALGICIN. Auralgicin—widely known, trusted and prescribed — alleviates pain, reduces the incidence of complications, promotes drainage and encourages resolution. It is quickly and easily administered. Instruction leaflets for the guidance of patients can be supplied to prescribers.

FULLY DESCRIPTIVE literature is available and a Technical Information Service is always at your disposal.

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A BENGER PRODUCT

Intramuscular Iron

and the

Anaemias of Infancy

The value of Imferon in Nutritional Anaemia of Infancy and in the prophylaxis and treatment of Anaemia of Prematurity has recently been convincingly demonstrated.

* "There was obvious rapid clinical improvement in all cases as shown by the return of appetite, change of disposition, improvement in colour, and gain in weight."

* "The daily rise in haemoglobin during the first two weeks after treatment was almost 1.5%."—*Lancet*, 1955, 2 700.

Imferon is the most practical and effective means of administering iron to infants who do not make progress on oral preparations. The increase in haemoglobin concentration is about 20% in two weeks—more than can be achieved with any form of oral therapy.

THE INDICATIONS FOR IMFERON IN INFANCY ARE:

1 Nutritional anaemia in infants who do not make progress on oral iron.
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4 As an alternative in some cases to blood transfusion.

FURTHER INFORMATION IS AVAILABLE ON REQUEST

Imferon is issued in ampoules of 2ml. (100 mg. Fe) in boxes of 10 and 100.

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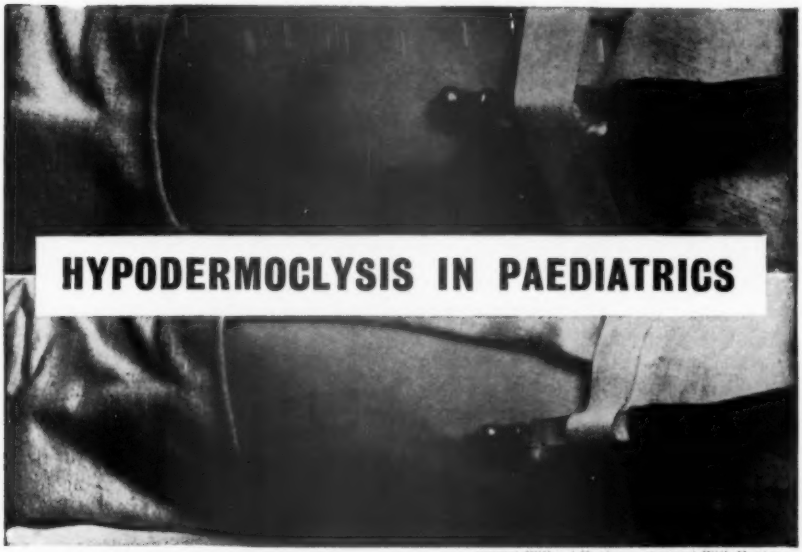

HYPODERMOCLYSIS IN PAEDIATRICS

(UPPER) *Without Hyalase.* (LOWER) *With Hyalase.*

INTRAVENOUS THERAPY may often be difficult owing to the inaccessibility of suitable veins or the restlessness of the child. Subcutaneous administration must be undertaken.

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Widespread Acceptance...

"The Iron given parenterally was absorbed from the intramuscular site and utilised."[1]

"Utilisation for haemoglobin production was extremely good."[2]

"In every patient a satisfactory rise in the haemoglobin took place."[3]

"... . all the patients in the series developed a vigorous sense of well-being which contrasted very strikingly with their previous chronic ill-health."[3]

"From the present series it appears that this new iron-dextran complex is a notable advance in the treatment of the iron-deficiency of pregnancy."[4]

1. LANCET, 1954, *2*, 942. 3. B.M.J., 1954, *2*, 1255.
2. B.M.J., 1954, *2*, 1257. 4. LANCET, 1954, *2*, 1245.

IMFERON IS THE FIRST EFFECTIVE IRON PREPARATION FOR INTRAMUSCULAR INJECTION.

IT PROVIDES the rapid, reliable response of an order hitherto only obtainable with intravenous preparations; and it takes much less time to administer.

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"It was obvious during this study that the skill and care of the person giving the injections does much to minimise local discomfort and staining, and it is significant that only two patients failed to attend for further injections."

(LANCET, 1954, *2*, 1245).

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IMFERON IRON-DEXTRAN COMPLEX

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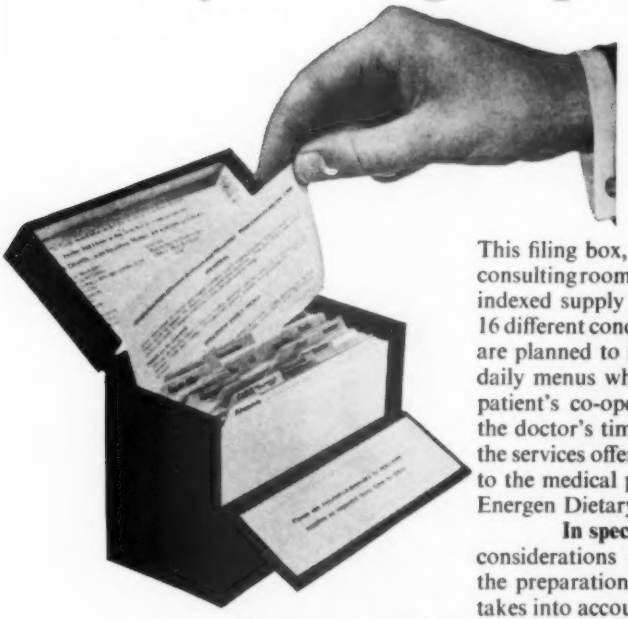
The right diet at your fingertips



This filing box, designed for the consulting room desk, contains an indexed supply of diet cards for 16 different conditions. The cards are planned to include specimen daily menus which facilitate the patient's co-operation and save the doctor's time. This is one of the services offered free of charge to the medical profession by the Energen Dietary Service.

In special cases, clinical considerations often necessitate the preparation of a diet which takes into account the individual requirements of the patient. On receipt of appropriate information from the practitioner, such diets can be specially constructed and sent through the post; or a consultation can be arranged with a senior dietitian.

The Energen Dietary Service is staffed by fully qualified dietitians, under close medical supervision. It offers independent information and assistance to the medical profession in all dietary and nutritional matters.

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Well in the lead...

Penicillin-V Lilly is an effective oral penicillin that is stable in the acid form and is not inactivated by gastric secretions. For the first time in oral penicillin therapy, clinical results produced are consistently comparable with treatment by parenteral penicillin.

When the case calls for penicillin let Penicillin-V Lilly—the penicillin that "passes the acid test"—be your choice.

The average dose is 0.5 Gm. daily—125 mg. four times in 24 hours, increased in severe infections.

Available as

'Pulvules' **125 mg.** (200,000 units), also 250 mg. and 60 mg. (Paediatric)

Suspension 62.5 mg. per 5 cc. For paediatric use.

and as TABLETS Penicillin-V-Sulpha, Lilly (Penicillin-V with Sulphonamides).

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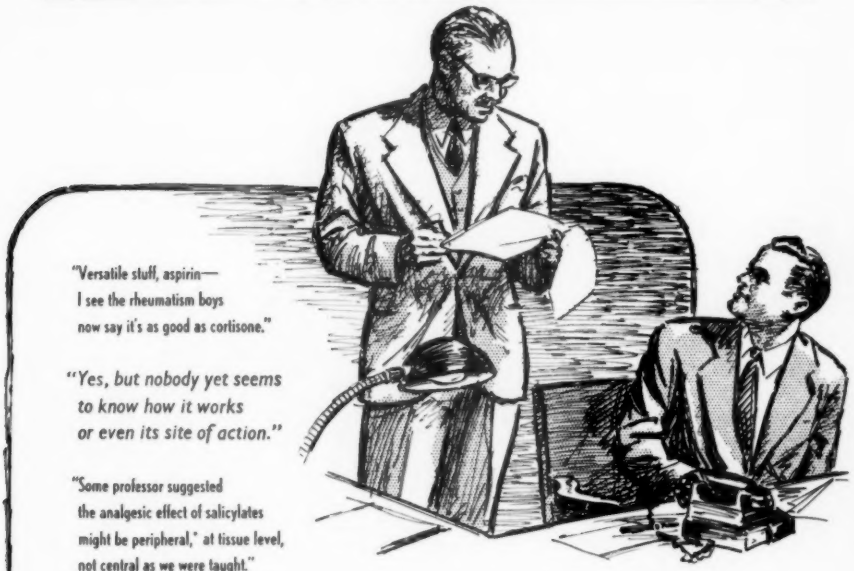

"Versatile stuff, aspirin—
I see the rheumatism boys
now say it's as good as cortisone."

*"Yes, but nobody yet seems
to know how it works
or even its site of action."*

"Some professor suggested
the analgesic effect of salicylates
might be peripheral," at tissue level,
not central as we were taught."

*"Could be. That reminds me—some firm has put up a new
skin-penetrating salicylate in a vanishing cream
for local tissue pain by inunction."*

"Does it work? And isn't it irritating?"

*"Yes and no. I've used it and it works well,
even in osteoarthritis. It's not irritating at all,
just a means of using salicylate locally."*

"Sounds promising. I'd like to try it. What is it called?"

* Practitioner, 178, 515 (1957)

Algesal

10% diethylamine salicylate in a soothing vanishing cream

**non-irritant, skin penetrating salicylate
for the relief of rheumatic pain by inunction**

Full literature and samples gladly sent on request to the manufacturers:
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"Versatile stuff, aspirin—
I see the rheumatism boys
now say it's as good as cortisone."

*"Yes, but nobody yet seems
to know how it works
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"Some professor suggested
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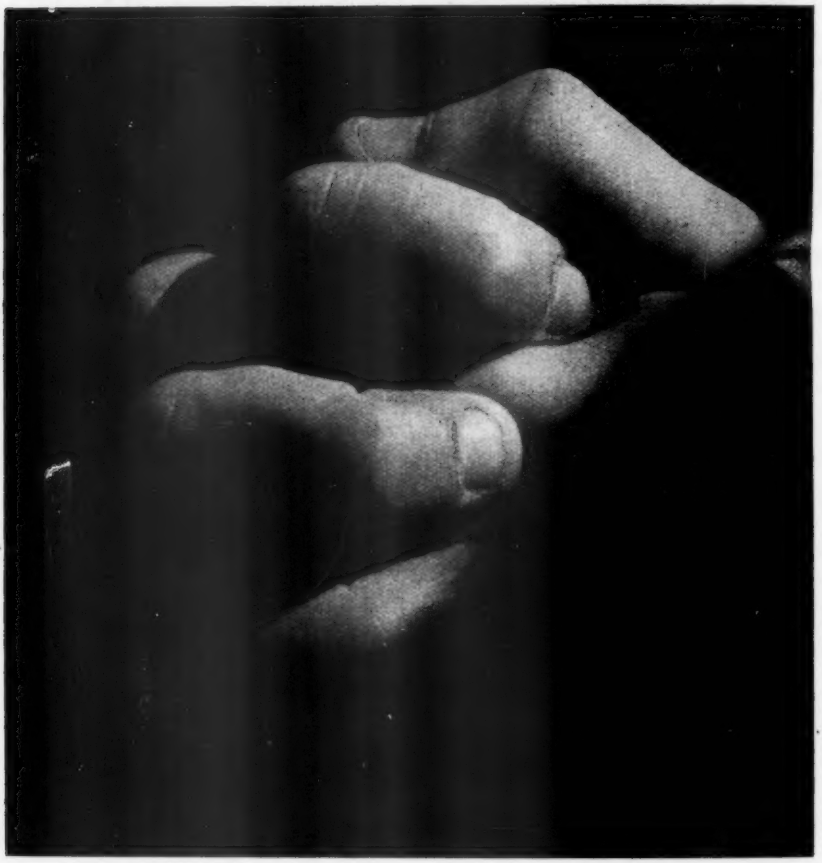
ASPECTS OF A CONDITION



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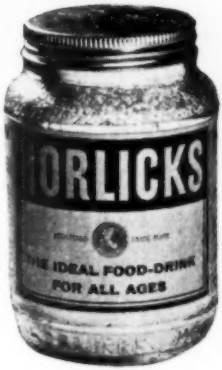
Horlicks is partially predigested and is suitable for patients of all ages.



ASPECTS OF A CONDITION

Bitten finger nails . . . mute witnesses to the conflict within the mind. Covatin provides daytime sedation without hypnosis. Covatin is to be preferred to phenobarbitone for it does not interfere with the alertness of the patient. Covatin is not habit-forming and has no side-effects. Covatin is available as 50 mg. sugar-coated tablets in bottles of 50 and 500.

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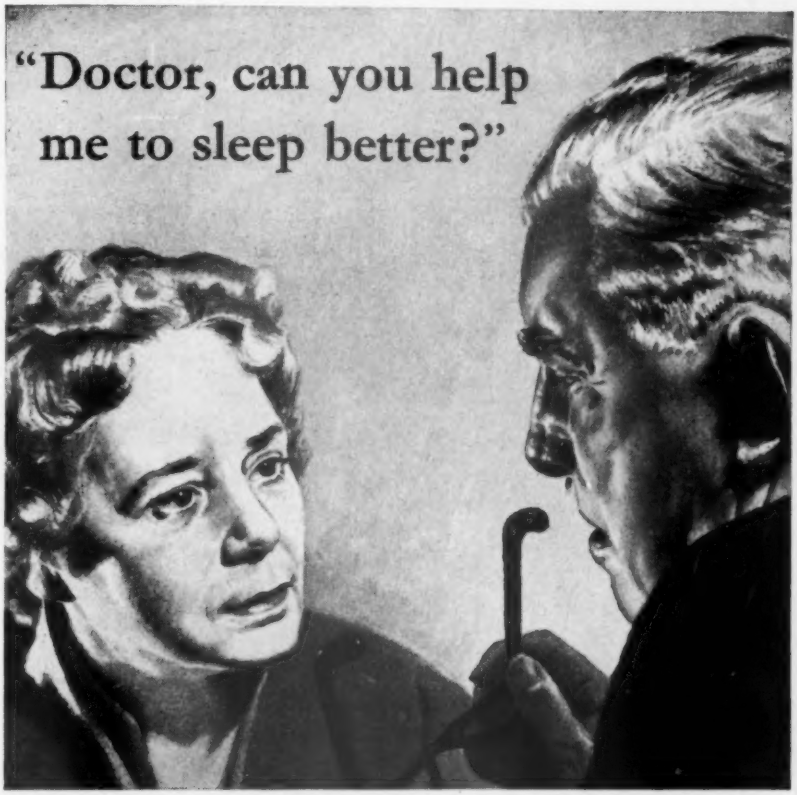

THE PATIENT who complains of uneasy sleep is often one of the doctor's most troublesome problems.

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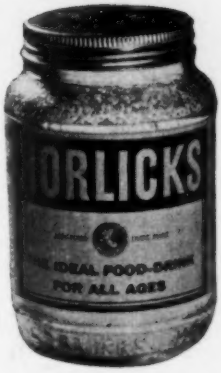

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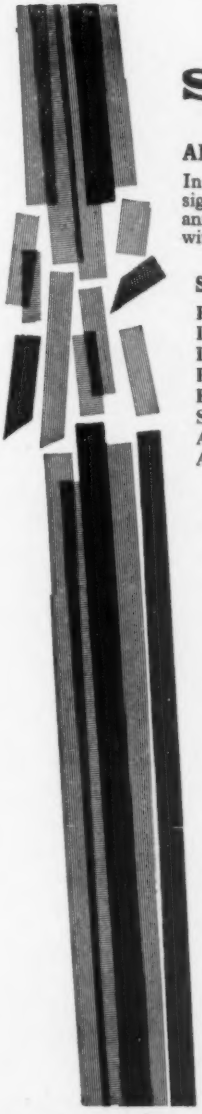

Stress

ANXIETY STATE — *aids to diagnosis*

In a recent medical article*, the following symptoms and signs were put forward as aids to the diagnosis of the anxiety state. They are not diagnostic, but in association with other observations may suggest the diagnosis.

SYMPTOMS

Headache (often localized in the back of the head and neck).
Inability to read or think (inability to concentrate).
Insomnia, dizziness
Palpitation and tachycardia
Faintness
Sense of tightness in the chest
} often resulting from hyperventilation.
Anorexia (common), **nausea, emesis, diarrhoea, aerophagia.**
Abdominal pain, backache, pain and stiffness in the shoulder region.

SIGNS

Sighing, wearing of tinted glasses, bitten fingernails.
Axillary perspiration.

AIDS TO TREATMENT

In the treatment of anxiety and tension, no one disputes the fundamental importance of the simple psychotherapy which the General Practitioner is so well placed to dispense. Yet he, himself, generally recognises the need for a more material adjunct, a tonic and restorative, which will assist the nervous system as well as the organism as a whole. Sanatogen is an active nutrient tonic, and the choice of many physicians in such circumstances. Conversely, the considerable effect of a poor nutritional state on the mental outlook has long been recognised. Here again, the merits of Sanatogen as a high protein tonic nutrient are apparent. Sanatogen contains 95% casein and 5% sodium glycerophosphate; because of its high nutrient value and tonic and restorative effects, it is beneficial in many forms of physical and mental debility.

* *Aust. N.Z. Gen. Practit.* (1955). *26*, 88.

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British Medical Journal, July 2nd 1955

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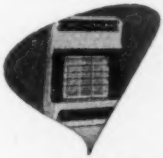

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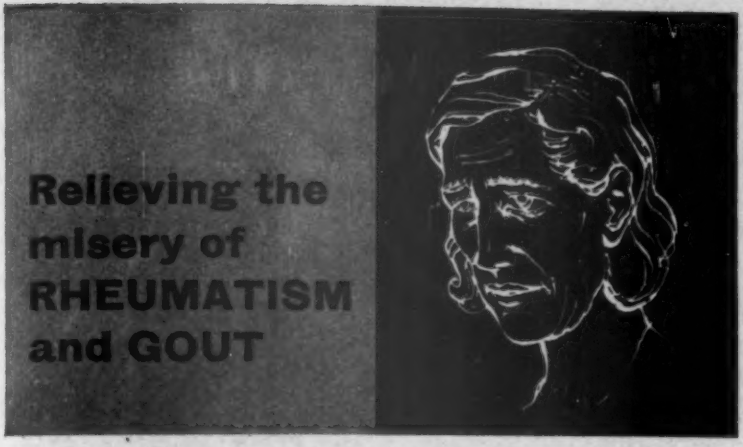

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